NEW YORK STATE BAR ASSOCIATION

FORM FOR VERIFICATION OF PRESENCE AT THIS PROGRAM

Pursuant to the Rules pertaining to the Mandatory Continuing Legal Education Program for Attorneys in the State of New York, as an Accredited Provider of CLE programs, we are required to carefully monitor attendance at our programs to ensure that certificates of attendance are issued for the correct number of credit hours in relation to each attendee's actual presence during the program. Each person may only turn in his or her form—you may not turn in a form for someone else. Also, if you leave the program at some point prior to its conclusion, you should check out at the registration desk. Unless you do so, we may have to assume that you were absent for a longer period than you may have been, and you will not receive the proper number of credits.

Speakers, moderators, panelists and attendees are required to complete attendance verification forms in order to receive MCLE credit for programs. Faculty members and attendees, please complete, sign and return this form to the registration staff **before you leave** the program.

PLEASE TURN IN THIS FORM AT THE END OF THE PROGRAM.

Food, Drug & Cosmetic Law Section Annual Meeting
Hot Topics in FDA Law
January 17, 2019 | New York Hilton Midtown, New York City

Name:_____
(please print)

I certify that I was present for the entire presentation of this program

Signature:_____Date:_____

Speaking Credit: In order to obtain MCLE credit for speaking at today's program, please complete and return this form to the registration staff before you leave. **Speakers** and **Panelists** receive three (3) MCLE credits for each 50 minutes of presenting or participating on a panel. **Moderators** earn one (1) MCLE credit for each 50 minutes moderating a panel segment. Faculty members receive regular MCLE credit for attending other portions of the program.

NYSBA

Hot Topics in FDA Law

Food, Drug & Cosmetic Law Section

January 17, 2019

New York Hilton Midtown

New York, NY

This program is offered for educational purposes. The views and opinions of the faculty expressed during this program are those of the presenters and authors of the materials, including all materials that may have been updated since the books were printed or distributed electronically. Further, the statements made by the faculty during this program do not constitute legal advice.

ACCESSING THE ONLINE ELECTRONIC COURSE MATERIALS

Program materials will be distributed online in PDF format. It is strongly recommended that you save the course materials in advance, in the event that you will be bringing a computer or tablet with you to the program.

Printing the complete materials is not required for attending the program.

The course materials may be accessed online at:
https://www.nysba.org/FDCMaterialsAM2019

A hard copy NotePad will be provided to attendees at the live program site, which contains lined pages for taking notes on each topic, speaker biographies, and presentation slides or outlines if available.

Please note:

- You must have Adobe Acrobat on your computer in order to view, save, and/or print the files. If you do not already have this software, you can download a free copy of Adobe Acrobat Reader at https://get.adobe.com/reader/
- If you are bringing a laptop, tablet or other mobile device with you to the program, please be sure that your batteries are fully charged in advance, as electrical outlets may not be available.
- NYSBA cannot guarantee that free or paid Wi-Fi access will be available for your use at the program location.

MCLE INFORMATION

Program Title: Food, Drug & Cosmetic Law Section Annual Meeting Program
Date/s:January 17, 2019 Location: New York, NY

Evaluation:

This evaluation survey link will be emailed to registrants following the program.

Total Credits: **5.5 New York CLE credit hours**

Credit Category:
5.5 Areas of Professional Practice

This course is approved for credit for **both** experienced attorneys and newly admitted attorneys (admitted to the New York Bar for less than two years). Newly admitted attorneys participating via recording or webcast should refer to www.nycourts.gov/attorneys/cle regarding permitted formats.

Attendance Verification for New York MCLE Credit

In order to receive MCLE credit, attendees must:

1) **Sign in** with registration staff
2) Complete and return a **Form for Verification of Presence** (included with course materials) at the end of the program or session. For multi-day programs, you will receive a separate form for each day of the program, to be returned each day.

Partial credit for program segments is not allowed. Under New York State Continuing Legal Education Regulations and Guidelines, credit shall be awarded only for attendance at an entire course or program, or for attendance at an entire session of a course or program. Persons who arrive late, depart early, or are absent for any portion of a segment will not receive credit for that segment. The Form for Verification of Presence certifies presence for the entire presentation. Any exceptions where full educational benefit of the presentation is not received should be indicated on the form and noted with registration personnel.

Program Evaluation

The New York State Bar Association is committed to providing high quality continuing legal education courses, and your feedback regarding speakers and program accommodations is important to us. Following the program, an email will be sent to registrants with a link to complete an online evaluation survey. The link is also provided above.

ADDITIONAL INFORMATION AND POLICIES

Recording of NYSBA seminars, meetings and events is not permitted.

Accredited Provider

The New York State Bar Association's **Section and Meeting Services Department** has been certified by the New York State Continuing Legal Education Board as an accredited provider of continuing legal education courses and programs.

Credit Application Outside of New York State

Attorneys who wish to apply for credit outside of New York State should contact the governing body for MCLE in the respective jurisdiction.

MCLE Certificates

MCLE Certificates will be emailed to attendees a few weeks after the program, or mailed to those without an email address on file. **To update your contact information with NYSBA**, visit www.nysba.org/MyProfile, or contact the Member Resource Center at (800) 582-2452 or MRC@nysba.org.

Newly Admitted Attorneys—Permitted Formats

Newly admitted attorneys (admitted to the New York Bar for less than two years) may not be eligible to receive credit for certain program credit categories or formats. For official New York State CLE Board rules, see www.nycourts.gov/attorneys/cle.

Tuition Assistance

New York State Bar Association members and non-members may apply for a discount or scholarship to attend MCLE programs, based on financial hardship. This discount applies to the educational portion of the program only. Application details can be found at www.nysba.org/SectionCLEAssistance.

Questions

For questions, contact the NYSBA Section and Meeting Services Department at SectionCLE@nysba.org, or the NYSBA Member Resource Center at (800) 582-2452 (or (518) 463-3724 in the Albany area).

NYSBA 2019 ANNUAL MEETING

Food, Drug and Cosmetic Law Section Hot Topics in FDA Law

Thursday, January 17, 2019 |1:00 p.m. - 6:00 p.m.

New York Hilton Midtown | Gibson Room, Second Floor

5.5 Credits

5.5 Areas of Professional Practice

This program is transitional and is suitable for all attorneys including those newly admitted.

Agenda

1:00 p.m. – 1:10 p.m. **Welcoming Remarks**

Brian J. Malkin, Section Chair | Arent Fox LLP, Washington, DC

1:10 p.m. – 2:25 p.m. **Overview of Biologic Policy Initiatives**

- What's new with specialty medications? (an examination of the biologics/biosimilars industry)
- Update on gene therapy
- Approvals in Europe/UK
- Payment models in the US and access to therapy
- Obstacles for future development of novel gene therapy products, including scientific, regulatory, and financial
- Wholesaler's perspective on their role with the supply chain including the payer community, as well as biological product supply chair evolution

Panelists:

Ronald W. Lanton, III, Esq. (Panel Chair)
Frier Levitt Government Affairs, LLC, Pine Brook, NJ

Sheila M. Arquette, R.PH.
Executive Director, National Association of Specialty Pharmacy, Washington, DC

Kelly A. Ryan
Senior Director, State Advocacy P*h*RMA, Albany, NY

Timothy Ward
President, Hercules Pharmaceuticals, Inc., Port Washington, NY

(1.5 Credits in Areas of Professional Practice)

2:25 p.m. – 2:30 p.m. **Refreshment Break**

2:30 p.m. – 3:45 p.m. **Medical Device Hot Topics: New Regulatory Models in Lab Developed Tests and Digital Health**

- Insights on FDA's 2018 "technical assistance" to Congress for LDT regulation
- New York State laboratory test oversight and FDA third party review framework
- FDA's evolving regulatory approach to digital health technologies
- Intersecting issues in diagnostics and digital health

Panelists:

Bethany J. Hills, Esq. (Panel Chair)
Mintz Levin, New York, NY

Aaron Josephson, M.S.
ML Strategies, LLC, Washington, DC

Lesley R. Maloney
Head of US Regulatory Policy, Roche Diagnostics, Washington, DC

	Howard A. Zucker, M.D., JD Commissioner, New York State Department of Health, Albany, NY
	(1.5 Credits in Areas of Professional Practice)
3:45 p.m. – 3:50 p.m.	**Refreshment Break**
3:50 p.m. – 4:15 p.m.	**Blockchain in Healthcare** **How Blockchain Can Be Used to Comply With the Drug Supply Chain Security Act**
Moderator:	**Larissa C. Bergin, Esq.** Jones Day, Washington, DC
Panelists:	**Combiz Richard Abdolrahimi, Esq.** Deloitte & Touche LLP, New York, NY
	Colleen M. Heisey, Esq. Jones Day, Washington, DC
	(*0.5 Credits in Areas of Professional Practice)*
4:15 p.m. – 4:40 p.m.	**GDPR Compliance: What You Need to Know**
Speaker:	**Amy B. Goldsmith, Esq.** (invited) Tarter Krinsky & Drogin, New York, NY
	(*0.5 Credits in Areas of Professional Practice)*
4:40 p.m. – 5:05 p.m.	***Helsinn v. Teva* and Secret Prior Art**
	When are secret sales and offers for sale prior art? How confidential agreements with third parties may invalidate your patents
Speaker:	**Janet B. Linn, Esq.** Tarter Krinsky & Drogin LLP, New York, NY
	(*0.5 Credits in Areas of Professional Practice)*
5:05 p.m. – 5:10 p.m.	**Refreshment Break**
5:10 p.m. – 5:35 p.m.	**Animal Testing Legislation**
Moderator:	**Thomas A. Cohn, Esq**. Director and Senior Counsel, Avon USA, New York, NY
Speaker:	**Sharon A. Blinkoff, Esq.** Lock Lorde LLP, New York, NY
	(*0.5 Credits in Areas of Professional Practice)*
5:35 p.m. – 6:00 p.m.	**Talcum Powder Products Litigation**
Moderator:	**Jennifer Orendi, Esq.** Managing Attorney, Dalimonte Rueb Litigation Group LLP, Washington, DC
Speaker:	**Victoria J. Maniatis, Esq.** Sanders Phillips Grossman, LLC, Garden City, NY
	(0.5 Credits in Areas of Professional Practice)
6:00 p.m. – 6:15 p.m.	**Food Drug & Cosmetic Law Section Annual Meeting, Business Meeting and Strategic Planning**
6:30 p.m. – 7:30 p.m.	**Off-Site Reception** Arent Fox LLP (next door to the Hilton) 1301 Avenue of the Americas, 42nd Floor New York, NY 10019

This program is co-sponsored by the New York Bar Foundation.

THE NEW YORK BAR FOUNDATION

SECTION CHAIR
Brian J. Malkin, Esq. | Arent Fox LLP | Washington, D.C.

Lawyer Assistance Program 800.255.0569

NYSBA

Q. What is LAP?

A. The Lawyer Assistance Program is a program of the New York State Bar Association established to help attorneys, judges, and law students in New York State (NYSBA members and non-members) who are affected by alcoholism, drug abuse, gambling, depression, other mental health issues, or debilitating stress.

Q. What services does LAP provide?

A. Services are **free** and include:

- Early identification of impairment
- Intervention and motivation to seek help
- Assessment, evaluation and development of an appropriate treatment plan
- Referral to community resources, self-help groups, inpatient treatment, outpatient counseling, and rehabilitation services
- Referral to a trained peer assistant – attorneys who have faced their own difficulties and volunteer to assist a struggling colleague by providing support, understanding, guidance, and good listening
- Information and consultation for those (family, firm, and judges) concerned about an attorney
- Training programs on recognizing, preventing, and dealing with addiction, stress, depression, and other mental health issues

Q. Are LAP services confidential?

A. Absolutely, this wouldn't work any other way. In fact your confidentiality is guaranteed and protected under Section 499 of the Judiciary Law. Confidentiality is the hallmark of the program and the reason it has remained viable for almost 20 years.

Judiciary Law Section 499 Lawyer Assistance Committees Chapter 327 of the Laws of 1993

Confidential information privileged. The confidential relations and communications between a member or authorized agent of a lawyer assistance committee sponsored by a state or local bar association and any person, firm or corporation communicating with such a committee, its members or authorized agents shall be deemed to be privileged on the same basis as those provided by law between attorney and client. Such privileges may be waived only by the person, firm or corporation who has furnished information to the committee.

Q. How do I access LAP services?

A. LAP services are accessed voluntarily by calling **800.255.0569** or connecting to our website **www.nysba.org/lap**

Q. What can I expect when I contact LAP?

A. You can expect to speak to a Lawyer Assistance professional who has extensive experience with the issues and with the lawyer population. You can expect the undivided attention you deserve to share what's on your mind and to explore options for addressing your concerns. You will receive referrals, suggestions, and support. The LAP professional will ask your permission to check in with you in the weeks following your initial call to the LAP office.

Q. Can I expect resolution of my problem?

A. The LAP instills hope through the peer assistant volunteers, many of whom have triumphed over their own significant personal problems. Also there is evidence that appropriate treatment and support is effective in most cases of mental health problems. For example, a combination of medication and therapy effectively treats depression in 85% of the cases.

Personal Inventory

Personal problems such as alcoholism, substance abuse, depression and stress affect one's ability to practice law. Take time to review the following questions and consider whether you or a colleague would benefit from the available Lawyer Assistance Program services. If you answer "yes" to any of these questions, you may need help.

1. **Are my associates, clients or family saying that my behavior has changed or that I don't seem myself?**
2. **Is it difficult for me to maintain a routine and stay on top of responsibilities?**
3. **Have I experienced memory problems or an inability to concentrate?**
4. **Am I having difficulty managing emotions such as anger and sadness?**
5. **Have I missed appointments or appearances or failed to return phone calls? Am I keeping up with correspondence?**
6. **Have my sleeping and eating habits changed?**
7. **Am I experiencing a pattern of relationship problems with significant people in my life (spouse/parent, children, partners/associates)?**
8. **Does my family have a history of alcoholism, substance abuse or depression?**
9. **Do I drink or take drugs to deal with my problems?**
10. **In the last few months, have I had more drinks or drugs than I intended, or felt that I should cut back or quit, but could not?**
11. **Is gambling making me careless of my financial responsibilities?**
12. **Do I feel so stressed, burned out and depressed that I have thoughts of suicide?**

There Is Hope

CONTACT LAP TODAY FOR FREE CONFIDENTIAL ASSISTANCE AND SUPPORT

The sooner the better!

1.800.255.0569

NEW YORK STATE BAR ASSOCIATION

☐ As a NYSBA member, **PLEASE BILL ME $25 for Food, Drug, and Cosmetic Law Section dues.** (law student rate is $12.50)

☐ I wish to become a member of the NYSBA (please see Association membership dues categories) and the Food, Drug, and Cosmetic Law Section. **PLEASE BILL ME for both.**

☐ I am a Section member — please consider me for appointment to committees marked.

Name _____

Address _____

_____

City _____ State _____ Zip _____

The above address is my ☐ Home ☐ Office ☐ Both

Please supply us with an additional address.

Name _____

Address _____

City _____ State _____ Zip _____

Office phone (_____) _____

Home phone (_____) _____

Fax number (_____) _____

E-mail address _____

Date of birth _____ /_____ /_____

Law school _____

Graduation date _____

States and dates of admission to Bar: _____

Food, Drug, and Cosmetic Law Section Committees

Please designate in order of choice (1, 2, 3) from the list below, a maximum of three committees in which you are interested. You are assured of at least one committee appointment, however, all appointments are made as space availability permits.

___ Biologics Law (FOOD1700)
Includes biologics, biosimilars, vaccines, & blood

___ Cosmetic Law (FOOD1800)

___ Diversity & Inclusion Committee (FOOD2500)

___ Drug Law (FOOD1400)
Includes prescription new drugs & generic drugs, OTC drugs

___ Food Law (FOOD1200)
Includes dietary supplements & human & animal food

___ Medical Device Law (FOOD1300)
Includes medical devices & radiation-emitting devices

___ Tobacco Law (FOOD2400)
FDA-regulated products & related issues

___ Animal Health Law (FOOD2000)
Note: does not include animal food, see food law

JOIN OUR SECTION

2019 ANNUAL MEMBERSHIP DUES

Class based on first year of admission to bar of any state. Membership year runs January through December.

ACTIVE/ASSOCIATE IN-STATE ATTORNEY MEMBERSHIP

Attorneys admitted 2011 and prior	$275
Attorneys admitted 2012-2013	185
Attorneys admitted 2014-2015	125
Attorneys admitted 2016 - 3.31.2018	60

ACTIVE/ASSOCIATE OUT-OF-STATE ATTORNEY MEMBERSHIP

Attorneys admitted 2011 and prior	$180
Attorneys admitted 2012-2013	150
Attorneys admitted 2014-2015	120
Attorneys admitted 2016 - 3.31.2018	60

OTHER

Sustaining Member	$400
Affiliate Member	185
Newly Admitted Member*	FREE

DEFINITIONS

Active In-State = Attorneys admitted in NYS, who work and/or reside in NYS
Associate In-State = Attorneys not admitted in NYS, who work and/or reside in NYS
Active Out-of-State = Attorneys admitted in NYS, who neither work nor reside in NYS
Associate Out-of-State = Attorneys not admitted in NYS, who neither work nor reside in NYS
Sustaining = Attorney members who voluntarily provide additional funds to further support the work of the Association
Affiliate = Person(s) holding a JD, not admitted to practice, who work for a law school or bar association
*Newly admitted = Attorneys admitted on or after April 1, 2018

Please return this application to:

MEMBER RESOURCE CENTER,
New York State Bar Association, One Elk Street, Albany NY 12207
Phone 800.582.2452/518.463.3200 • FAX 518.463.5993
E-mail mrc@nysba.org • www.nysba.org

Overview of Biologic Policy Initiatives

Ronald W. Lanton, III, Esq.
Frier Levitt Governmental Affairs, LLC | Pine Brook, NJ

Sheila M. Arquette, R.PH.
National Association of Special Pharmacy | Washington, DC

Mary Jo Carden
Academy of Managed Care Pharmacy | Washington, DC

Timothy Ward
Hercules Pharmaceuticals, Inc. | Port Washington, NY

Kelly A. Ryan
State Advocacy PhRMA | Albany, NY

Sheila Arquette, RPH
Executive Director

Who is NASP?

- The National Association of Specialty Pharmacy- NASP (www.naspnet.org) is the only national association representing all stakeholders in the specialty pharmacy industry.
- The core mission of NASP is to provide educational programs to pharmacists and other healthcare professionals and to promote specialty pharmacist certification for those working in specialty pharmacy.
- NASP is committed to educating and advocating on behalf of its multi-stakeholder membership to ensure specialty patients receive high quality patient care services from the pharmacy of their choosing and to transform the delivery of specialty healthcare through active engagement with improving the patient experience, enhanced clinical outcomes and by fostering the education and certification of pharmacists focused on specialty drug /disease management.

- NASP provides an online education center, with over 45 continuing pharmacy education programs, hosts an annual educational conference and expo that offers education sessions and continuing education credits, and is the only organization that offers a certification program for specialty pharmacists.
- NASP members include the nation's leading independent specialty pharmacies, pharmaceutical and biotechnology manufacturers, group purchasing organizations, patient advocacy groups, integrated delivery systems and health plans, technology and data management vendors, wholesalers/distributors and practicing pharmacists
- With over 100 corporate members and 1,500 individual members, NASP is the unified voice of specialty pharmacy in the United States.
- Not all NASP members are pharmacists but all in some way touch the specialty pharmacy patient along the patient care journey.

What is a Biosimilar?

- A **biosimilar** (also known as **follow-on biologic** or **subsequent entry biologic**) is a biologic medicine that is almost an identical copy of an original product that is manufactured by a different company.
- Biosimilars are officially approved versions of original "innovator" products and can be manufactured when the original product's patent expires.
- Reference to the innovator product is an integral component of the approval.
- Unlike with generic copies of the more common small molecule drugs, biologics generally exhibit high molecular complexity and may be quite sensitive to changes in manufacturing processes.
- Biosimilars must maintain consistent quality and clinical performance throughout their lifecycle.
- Follow-on manufacturers do not have access to the originator's molecular clone and original cell bank, to the exact fermentation and purification process, or to the active drug substance, but they have access to the commercialized innovator product.
- Overall, it is harder to establish interchangeability between biosimilars and innovators than it is among fully synthesized or semisynthesized generic copies of brand name drugs . That is why the name "biosimilar" was coined to differentiate them from small-molecule generics.
- A simple analogy, often used to explain the difference, is to compare wine with soda pop. It is harder to say objectively that two bottles of wine made from the same grape variety from two wineries are "sufficiently interchangeable," because of differences in yeast strain, weather, conditions, and year of grape harvest, than it is to say that two bottles of orange soda pop coming from two different bottling facilities are "sufficiently interchangeable" because they contain the same flavoring powder.

Biosimilar Overview

- Legislation
  - The Biologics Price Competition and Innovation Act of 2009 (BPCI Act) was originally sponsored and introduced in 2007, by Senator Edward Kennedy (D-MA).
  - It was formally passed under PPACA in 2010
  - The BPCI Act created an abbreviated approval pathway for biological products that are demonstrated to be highly similar (biosimilar) to FDA approved biological product.
  - The BPCI Act aligns with the FDA's longstanding policy of permitting appropriate reliance on what is already known about a drug, thereby saving time and resources and avoiding unnecessary duplication of human or animal testing.
  - Provides 12-year patent protection on data exclusivity
  - Established 351(k) filing process vs 351(a) application filing
  - Single reference product against which a proposed biosimilar product is compared

- The global biosimilars market was $1.3 billion in 2013
- 12 biologic products with global sales >$67 billion may face biosimilar competition by 2020
- U.S. is behind Europe and Asia in biosimilar regulations and number of approved products
- The "Purple Book" lists biological products, including any biosimilar and interchangeable biological products, licensed by FDA under the Public Health Service Act.
- FDA approval does not mean a product will launch immediately; there may be substantial delays in launch due to patent law disputes

- Products may be approved as biosimilar to the reference product or as interchangeable
  - Interchangeable product is a biosimilar product that meets additional requirements outlined by the BPCI Act. As part of fulfilling these additional requirements, information is needed to show that an interchangeable product is expected to produce the same clinical result as the reference product in any given patient.
  - only a biologic that has been approved as an interchangeable may be substituted for the reference product without the intervention of the health care provider who prescribed the reference product.
- Percentage price reduction for biosimilars so far has been less than for small molecule drug generics
- Prices likely to decrease as the number of launched biosimilars increases
- Utilization will depend on price, reimbursement methodology, payor considerations, patient and prescriber comfort level with biosimilars, patient cost share

U.S. Approved Biosimilars

Date of Biosimilar FDA Approval		Original Product
March 6, 2015	filgrastim-sndz/Zarxio	filgrastim/Neupogen
April 5, 2016	infliximab-dyyb/Inflectra	infliximab/Remicade
August 30, 2016	etanercept-szzs/Erelzi	etanercept/Enbrel
September 23, 2016	adalimumab-atto/Amjevita	adalimumab/Humira
April 21, 2017	infliximab-abda/Renflexis	infliximab/Remicade
August 25, 2017	adalimumab-adbm/Cyltezo	adalimumab/Humira
September 14, 2017	bevacizumab-awwb/Mvasi	bevacizumab/Avastin
December 1, 2017	trastuzumab-dkst/Ogivri	trastuzumab/Herceptin
December 13, 2017	infliximab-qbtx/Ixifi	infliximab/Remicade
May 15, 2018[5]	epoetin alfa-epbx/Retacrit	epoetin alfa/Procrit
June 4, 2018	pegfilgrastim-jmdb/Fulphila	pegfilgrastim/Neulasta
November 28, 2018 December 18, 2018	rituximab-abbs/Truxima Trastuzumab-pkrb/Herzuma	rituximab/Rituxan Trastuzumab/Herceptin

Opportunities for Specialty Pharmacy

- Most cost effective alternatives for patients with larger cost share liabilities
  - Improved affordability may increase patient access to biologic drug treatment
  - Increased compliance and adherence
  - Enhanced clinical outcomes
- Medication Resource for prescribers and patients
- Data collection

Payor Response

- Uptake has been slow
- Biosimilar pricing has only been 10-15% less than the reference product
- The Rebate Effect
- Other Confounding factors:
  - Patient and prescriber education and acceptance
    - According to a 2014 survey, almost 30% of people living with a diagnosis said that their medicinal choice was highly influenced by the drug manufacturer's identity.
    - Prescribers may see biosimilars as extra work: review clinical data, discuss substitution with pharmacists, work through potential coverage barriers,
  - Extrapolation issue
    - granting a clinical indication to a medication without its own or new clinical safety and efficacy studies to support that indication". Whether biosimilars can be prescribed for off-label indications, that are okayed for the reference drug, is a grey area. If insurers, hospitals and pharmacies are forced to cover and stock both the reference molecule as well as the biosimilar counterpart this nullifies the cost benefits from prescribing the biosimilar.
  - Product switching
    - Will stable patients level of disease control be compromised and the resulting impact

Contact Information

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AMCP Activity on Biosimilars

Overview and Strategy

R901481478

Mary Jo Carden, RPh, JD
mcarden@amcp.org
Vice President, Government and Pharmacy Affairs
Academy of Managed Care Pharmacy
Alexandria, Virginia

January 17, 2019

AMCP Academy of Managed Care Pharmacy

AMCP is the nation's leading professional association dedicated to increasing patient access to affordable medicines, improving health outcomes and ensuring the wise use of health care dollars.

Through evidence- and value-based strategies and practices, the Academy's 8,000 pharmacists, physicians, nurses and other practitioners manage medication therapies for the 270 million Americans served by health plans, pharmacy benefit management firms, emerging care models and government.

AMCP Academy of Managed Care Pharmacy

AMCP Biosimilars Position

- **Pathway** – expedited FDA approval process
- **Naming** – same government-approved name/INN as reference product
- **Interchangeability** – FDA should implement a 2-step process that determines:
  - (1) biosimilarity
  - (2) interchangeability
- **Clinical Trials** – FDA case-by-case determination

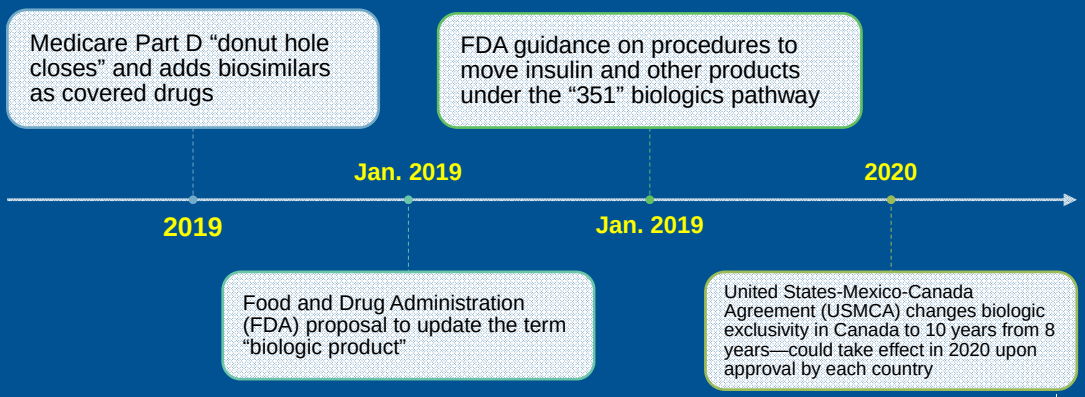
AMCP Academy of Managed Care Pharmacy

Overview of Actions on Biosimilars

- Brief history of biosimilar policy
- Notable federal and state action on biosimilars
- AMCP activity

AMCP Academy of Managed Care Pharmacy

Notable Recent Actions on Biosimilars



AMCP Academy of Managed Care Pharmacy

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"I am worried that there are either deliberate or unintentional efforts by branded companies to create confusion. . ."

The messages "can potentially undermine consumer confidence in biosimilars in ways that are untrue."

FDA Commissioner Scott Gottlieb
Interview with the *Washington Post*

Rowland, C. 'Marketers are having a field day': Patients stuck in corporate fight against generic drugs. *Wash. Post.* January 9, 2019. https://www.washingtonpost.com. Accessed January 11, 2019.

AMCP Academy of Managed Care Pharmacy

Biosimilars Action Plan – FDA released July 2018

- Key Elements
  - Improving the efficiency of the biosimilar and interchangeable product development and approval process
  - Maximizing scientific and regulatory clarity for the biosimilar product development community
  - Developing effective communications to improve understanding of biosimilars among patients, clinicians, and payors
  - Supporting market competition by reducing gaming of FDA requirements or other attempts to unfairly delay competition.
  - Finalizing or Revising Guidance central to FDA's plan

https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm613761.pdf

AMCP Academy of Managed Care Pharmacy

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FDA Biosimilar Action Plan

- Strategies include:
  - Combating unfair practices in intellectual property law and the REMS program which lead to decreased access to samples for approval testing,
  - Streamlining the regulatory and approval processes that FDA has direct jurisdiction over
  - Moving some biologics and biosimilars from Medicare Part B to Part D,
    - AMCP supports this move, which we discussed in our comments to the HHS Drug Pricing Blueprint RFI

https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm613761.pdf

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8

State Biosimilar Legislation

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9

Biosimilar and Interchangeable Drug Products Legislation and Laws

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State Activity on Biosimilars and Interchangeables

- Began legislating in 2013 before any applications for biosimilar approval were filed in the U.S. – first one not approved until March 2015
- Most states do not recognize interchangeable products as defined by the BPCIA may be substituted by pharmacist without intervention of the provider
- Requires electronic communication not all pharmacies/prescribers linked in EHR – and won't be for a while – other means require more pharmacist time
- Added requirements could impact prescriber/patient confidence in the products and slow and or stop market uptake of biosimilars
- Require use of the Orange Book instead of the Purple Book designated by FDA as the resource for biosimilarity and interchangeability evaluations

AMCP Academy of Managed Care Pharmacy

AMCP Activity

AMCP Academy of Managed Care Pharmacy

12

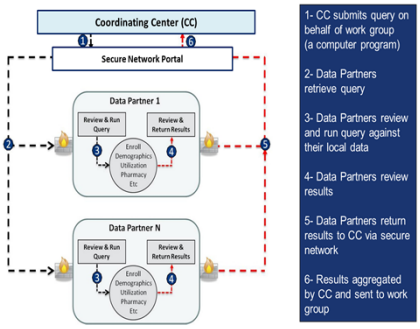
BBCIC Surveillance –Leveraging Sentinel Capabilities

The AMCP Biologics and Biosimilars Collective Intelligence Consortium's strategy provides a unique opportunity for Managed Care to support public knowledge of biologic and biosimilar drugs with robust science.

BBCIC leverages the Sentinel Initiative → Improves the efficiency and cost-effectiveness of post-marketed observational studies.

BBCIC actively monitors biosimilars and innovators → Anonymous data from ~150 million patients

BBCIC is a multi-stakeholder collaboration → Diverse expertise allows for a larger voice with more credibility



1- CC submits query on behalf of work group (a computer program)

2- Data Partners retrieve query

3- Data Partners review and run query against their local data

4- Data Partners review results

5- Data Partners return results to CC via secure network

6- Results aggregated by CC and sent to work group

A forum for collaboration between managed care organizations, integrated delivery networks, PBMs, pharma companies and research institutions

www.amcp.org

AMCP Academy of Managed Care Pharmacy®

Biosimilars Resource Center

NCPA National Community Pharmacists Association · NASPA · HOPA Hematology/Oncology Pharmacy Association · ASCP American Society of Consultant Pharmacists · American Association of Colleges of Pharmacy AACP · American Pharmacists Association APhA · AHIP America's Health Insurance Plans

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AMCP's Path Forward

- AMCP should partner with FDA and others to provide education on safety and efficacy of biosimilars and interchangeable biologic products
  - Focus on education that interchangeability does not require physician consultation by a pharmacist
- FDA should release interchangeability guidance with reasonable standards
- AMCP should promote the work of BBCIC and its role in gathering real-world evidence on biologics and biosimilars

AMCP Academy of Managed Care Pharmacy

Why is Education Important?

What We Don't Know Will Hurt Us

Uncertainty about safety and efficacy among consumers and providers stymie adoption

We've seen this before: Lack of understanding resulted in slow initial adoption of generics in the 1980s

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Supply Chain for Biosimilars

Ethical, Secured & Accredited

Executive Summary

- Licensed, regulated & authorized entities may only conduct transactions between themselves with the concurrent responsibilities that (i) they ensure counterparties are licensed and authorized, (ii) the goods are moved and stored pursuant to their environmental threshold, (iii) inspected at each step to ensure ‘suspect product’ and ‘illegitimate product’ does not enter into our supply, (iv) that the transactional information is documented and retrievable pursuant to regulatory requirements. This ensures that all medicine **dispensed** or **administered** to patients are of the utmost quality.
- Overlapping federal and state regulations combined with industry accreditation combine to set the standards.

Definitions

Definition of Biologics

- Biologics include a wide range of products such as vaccines, blood and blood components, allergenics, somatic cells, gene therapy, tissues, and recombinant therapeutic proteins.[1]
- Biologics can be composed of sugars, proteins, or nucleic acids or complex combinations of these substances, or may be living entities such as cells and tissues.[1]
- Biologics are isolated from a variety of natural sources - human, animal, or microorganism - and may be produced by biotechnology methods and other cutting-edge technologies.[1]
- Gene-based and cellular biologics, for example, often are at the forefront of biomedical research, and may be used to treat a variety of medical conditions for which no other treatments are available.[1]
- Biologics is one of the fastest growing sectors of cancer treatment[3]

Definitions

Definition of Biosimilars

Biosimilar is a copy of a commercially available biologic (reference product*) that is no longer protected by patent[4]

- It has undergone rigorous analytical and clinical assessment in comparison to its reference product[4]
- It is highly similar to and has no clinically meaningful differences from an existing FDA-approved reference product[2]
- It has been approved by a regulatory agency according to a specific pathway for biosimilar evaluation[4]

*A reference product is the single biological product, already approved by FDA, against which a proposed biosimilar product is compared[2].

Importance of Biosimilars

- Biological products often represent the cutting-edge of biomedical research and, in time, may offer the most effective means to treat a variety of medical illnesses and conditions that presently have no other treatments available[1].
- As the costs of biologics are high, biosimilars offer the potential of greater choice and value, increased patient access to treatment, and the potential for improved outcomes[3].
- Biosimilars may provide an important tool for providers participating in value-based care initiatives, resulting in cost savings and efficiencies in the delivery of high-value care through expanded use of biologic treatment and supportive care agents during episodes of cancer care[3]

Footnote:

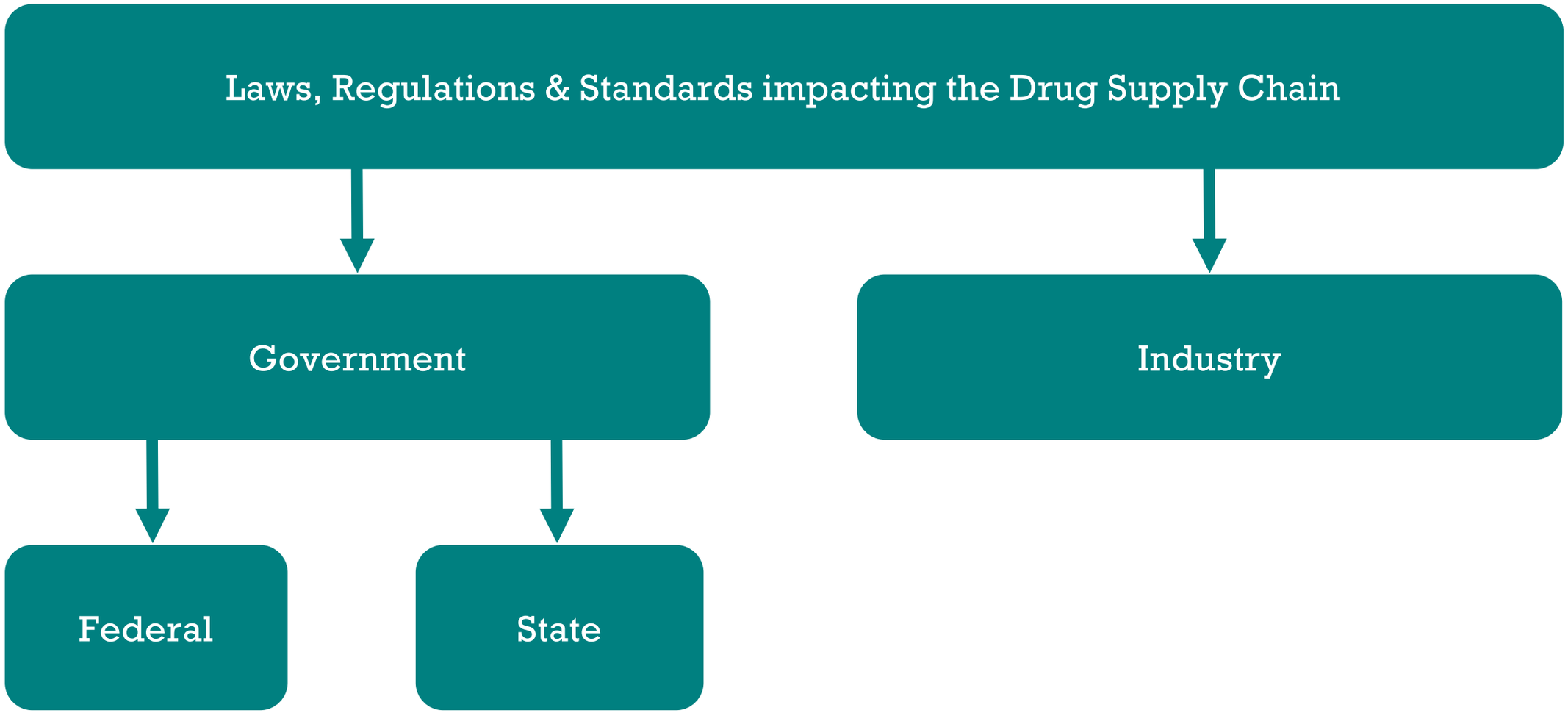
1 " What Are "Biologics" Questions and Answers", US Food & Drug Administration https://www.fda.gov/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cber/ucm133077.htm

2 "Biosimilar and Interchangeable Products", US Food & Drug Administration. https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapEUticBiologicApplications/Biosimilars/ucm580419.htm#biological

3 Patel K, Arantes L, et al. The role of Biosimilars in value-based oncology care. Dove Press Journal: Cancer Management and Research 2018:10.

4 Patel K. "Biosimilars in the USA and Part B Drug Prices"

Regulatory Structure

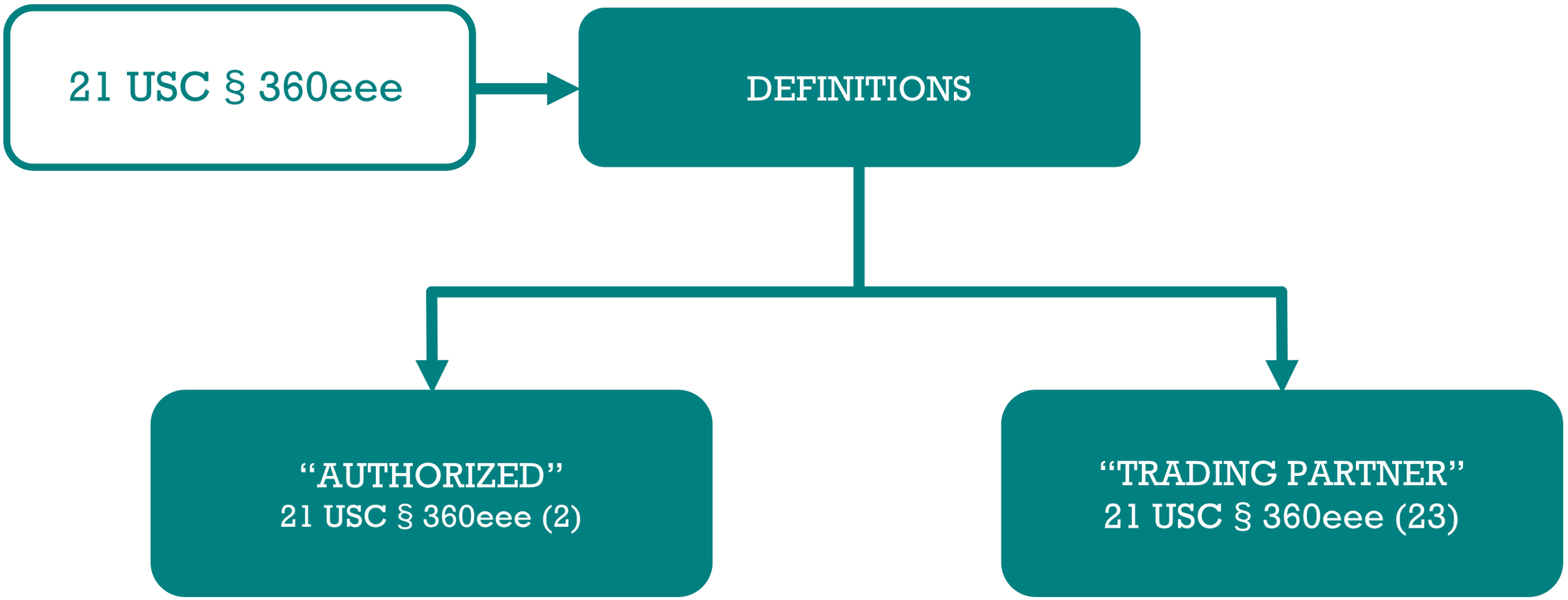


Federal Regulation

Drug Supply Chain Security Act (DSCSA)

- Title II of the Drug Quality and Security Act (DQSA)

Subchapter H - Pharmaceutical Distribution Supply Chain



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“Authorized”

Manufacturer / Repackager

21 USC § 360eee (2)(a)

- **Manufacturer** or repackager, having a valid registration in accordance with section 360 of this title.

Wholesale Distributor

21 USC § 360eee (2)(b)

- **Wholesale Distributor**, having a valid license under State law or section 360eee–2 of this title, in accordance with section 360eee–1(a)(6) of this title, and complying with the licensure reporting requirements under section 353(e) of this title

Third party logistics provider (3PL)

21 USC § 360eee (2)(c)

- A **third-party logistics provider**, having a valid license under State law or section 360eee–3(a)(1) of this title, in accordance with section 360eee–1(a)(7) of this title, and complying with the licensure reporting requirements under section 360eee–3(b) of this title

Dispenser

21 USC § 360eee (2)(d)

- A **dispenser**, having a valid license under State law

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“Trading Partner”

Trade, Transactions & incidents to trade and transactions must occur amongst and between authorized trading partners

21 USC § 360eee (23)

(23) Trading partner - The term “trading partner” means:

(A) a **manufacturer**, repackager, **wholesale distributor**, or dispenser from whom a manufacturer, repackager, wholesale distributor, or dispenser accepts direct ownership of a product or to whom a manufacturer, repackager, wholesale distributor, or dispenser ***transfers direct ownership*** of a product

(B) a **third-party logistics provider** (does not take ownership of the product, nor have responsibility to direct the sale or disposition of the product”)

(24) Transaction (A) In general The term **“transaction”** means the transfer of product between persons in which a change of ownership occurs.

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“Trading Partner”

“not later than January 1, 2015, the ***trading partners*** of a [ ] ***may be only authorized trading*** partners”

- Manufacturers — 21 USC § 360eee1(b)(3)
- Wholesale Distributors — 21 USC § 360eee1(c)(3)
- Dispensers — 21 USC § 360eee1(d)(3)
- Repackager — 21 USC § 360eee1(e)(3)

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Transition to State Regulation

Authorized Trading Partners

21USC353(e) Licensing and reporting requirements for wholesale distributors; fees; definitions

(1)Requirement. - Subject to section 360eee–2 of this title:

(A)In general. - No person may engage in wholesale distribution of a drug subject to subsection **(b)(1)** in any State unless such person -
(i) (I) is licensed by the State from which the drug is distributed; or
(II) …
(ii) if the drug is distributed interstate, is licensed by the State into which the drug is distributed if the State into which the drug is distributed requires the licensure of a person that distributes drugs into the State.

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“Dispenser”

21USC360eee(3) Dispenser The term **“dispenser”** - (A) means a … pharmacy … or any other person authorized by law to ***dispense*** or ***administer prescription drugs***, and the affiliated warehouses or distribution centers of such entities under common ownership and control that do not act as a **wholesale distributor**; and

- **Example~ Pharmacy (Alabama)**
  Under Alabama law pharmacies shall register biennially and receive a permit from the board. Ala.Code 1975 § 34-23-30.

- **Example~ Dispensing Physician**
  General Authority (Arkansas) A dispensing physician is a physician licensed under the Arkansas Medical Practices Act, §17-95-201 et seq., §17-95-301 et seq., and §17-95-401 et seq., who purchases legend drugs to be dispensed to his or her patients for the patients' personal use and administration outside the physician's office. A.C.A. §17-95-102. A physician's license is required.
  Specific Authority (Florida) “ … a practitioner authorized by law to prescribe drugs may dispense such drugs to her or his patients in the regular course of her or his practice in compliance with this section”. West's F.S.A. §465.0276 (1)(a). A dispensing practitioner must register with her or his professional licensing board as a dispensing practitioner. West's F.S.A. §465.0276 (2)(a). A dispensing license is required in addition to a general medical license.

- **Example~ Administering Physician (North Carolina)**
  Under North Carolina law, the practice of medicine includes … administer[ing] any drug or medicine …. N.C. Gen. Stat. §90-1.1. Administer is defined as the direct application of a drug to the body of a patient …. N.C. Gen. Stat. §90-85.3. Must have a valid North Carolina Medical License. N.C. Gen. Stat. §90-1.1. A general medical license is required.

Track & Trace Documentation

21USC360eee(25) Transaction history The term "transaction history" means a statement in paper or electronic form, including the transaction information for each prior transaction going back to the manufacturer of the product.

21USC360eee(26) Transaction information. The term "transaction information" means:

(A) the proprietary or established name or names of the product;

(B) the strength and dosage form of the product;

(C) the National Drug Code number of the product;

(D) the container size;

(E) the number of containers;

(F) the lot number of the product;

(G) the date of the transaction;

(H) the date of the shipment, if more than 24 hours after the date of the transaction;

(I) the business name and address of the person from whom ownership is being transferred; and

(J) the business name and address of the person to whom ownership is being transferred.

(27) Transaction statement. The "transaction statement" is a statement, in paper or electronic form, that the entity transferring ownership in a transaction—

21USC360eee(27) Transaction statement. The "transaction statement" is a statement, in paper or electronic form, that the entity transferring ownership in a transaction—

(A) is authorized as required under the Drug Supply Chain Security Act;

(B) received the product from a person that is authorized as required under the Drug Supply Chain Security Act;

(C) received transaction information and a transaction statement from the prior owner of the product, as required under section 360eee–1 of this title;

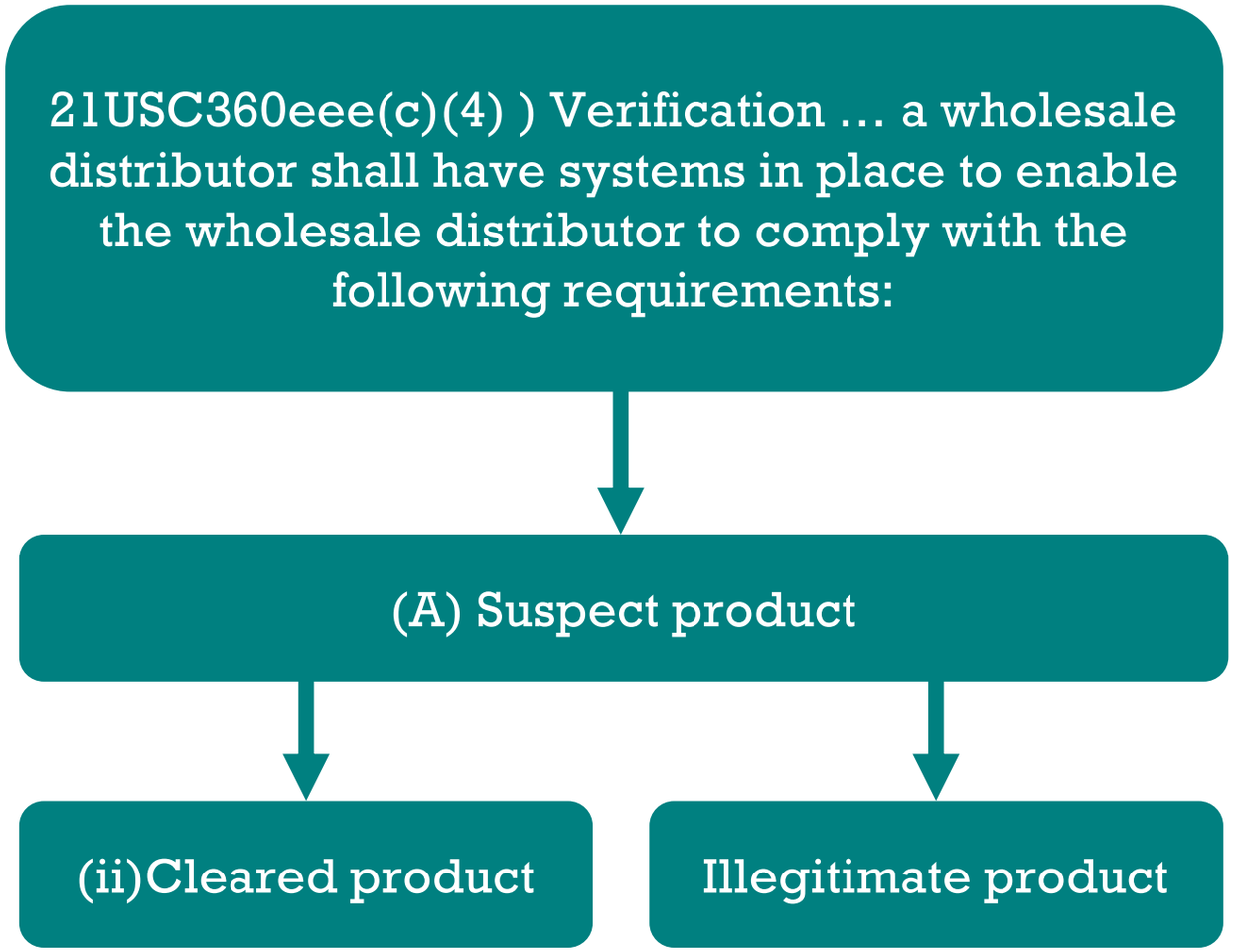
(D) did not knowingly ship a suspect or illegitimate product;

(E) had systems and processes in place to comply with verification requirements under section 360eee–1 of this title;

(F) did not knowingly provide false transaction information; and

(G) did not knowingly alter the transaction history.

Suspect Product Analysis



21USC360eee(21) Suspect product

The term "suspect product" means a product for which there is reason to believe that such product -

(A) is potentially counterfeit, diverted, or stolen;

(B) is potentially intentionally adulterated such that the product would result in serious adverse health consequences or death to humans;

(C) is potentially the subject of a fraudulent transaction; or

(D) appears otherwise unfit for distribution such that the product would result in serious adverse health consequences or death to humans.

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Illegitimate Product

21USC360eee(8) Illegitimate product. The term **"illegitimate product"** means a product for which credible evidence shows that the product -

(A) is counterfeit, diverted, or stolen;

(B) is intentionally adulterated such that the product would result in serious adverse health consequences or death to humans;

(C) is the subject of a fraudulent transaction; or

(D) appears otherwise unfit for distribution such that the product would be reasonably likely to result in serious adverse health consequences or death to humans.

21USC360eee(c)(4)(B)

(i) [for an] illegitimate product, the wholesale distributor shall … -

(I) quarantine such product … ;

(II) disposition the illegitimate product …;

(III) …assist a trading partner to disposition an illegitimate product not in the possession or control of the wholesale distributor; and

(IV) retain a sample… as necessary and appropriate.

(ii) Making a notification… the wholesale distributor shall notify the Secretary and … trading partners … [within]24 hours

(iii) Responding to a notification …

(v) Records

A wholesale distributor shall keep records of the disposition of an illegitimate product for not less than 6 years after the conclusion of the disposition.

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Accreditation

Industry Standards Set By the National Association of Boards of Pharmacy (NABP) through its The Verified-Accredited Wholesale Distributors® (VAWD®) accreditation

NABP
NATIONAL ASSOCIATION OF BOARDS OF PHARMACY

NATIONAL ASSOCIATION VAWD BOARDS OF PHARMACY

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Refrigeration

HDA

Standard Pharmaceutical Product Information (Rx Product Only)

Introduction Type: ☑ Final Version **Date:** 10/24/2018

Product Information

Company Name:	Mylan Pharmaceuticals	**Application:**	ANDA
Application Number for NDA/ANDA/BLA/Med Device	206936		
Rx Product Proprietary Name	Glatiramer Acetate Injection, 40 mg/mL Prefilled Syringe		
NDC:	0378-6961-12	**UPC:**	00303786961122
CVX Code:		**MVX Code:**	
Description:	Glatiramer Acetate Injection, 40 mg/mL Prefilled Syringe		
Active Ingredients:	Glatiramer Acetate		
URL for Additional Product Information:	http://www.mylan.com/		
Address:	781 Chestnut Ridge Road	**Address 2:**	
City:	Morgantown	**State:** WV	**Zip:** 26505
Key Contact:	Customer Relations	**Email:**	customer.service@mylan.com
Phone Number:	800.796.9526	**Fax:**	304.285.6418

For Generic Drug Products

I. Orange Book Rating AP **II: Brand Name** Copaxone®

III. Generic Equivalent For Brand n/a

Drug Supply Chain Security Act (DCSA) Information

Does supplier meet DSCSA definition of manufacturer ?	Yes	**DUNS:**	059295980
Is product exempt from DCSA?	No		
If yes, select exemption	N/A		
Other Exemption-Write In			
Is product Repackaged?	No	**if yes, was product purchased direct from mfr.?**	N/A
Is product sold by manufacturer's exclusive distributor?	No		
Are any waivers granted for product ID/barcode?	No	**If yes, attach documentation from FDA**	

Special Handling and Storage Requirements*

a. Storage Conditions

KEEP REFRIGERATED (2° to 8°C/36° to 46°F) AND PROTECT FROM LIGHT.

b. Contact for temperature excursion questions:

Name: Customer Relations

Number: 800.796.9526

Is this product to be shipped to customers on ice?

is this product to be shipped to customers on dry ice?

c. Special Regulations for product in Certain States?

Special returns requirements for this product?

d. Store prduct (unit of sale) upright?

Protect product (unit of sale) from light? Yes

e. Shelf life 24 **Months**

Initial Shelf life at launch (if different):

Additional Product Information

Is the Product...	
Legend Device?	
State Control?	No
ARCOS Reportable	No
Co-Licensed	
Controlled Substance?	No
Schedule No.?	-
Controlled Substance Code:	-
Hazardous Material/Cytotixic Agent	
Is Item....	No
If Unit Dose, is item bar coded to unit dose for hospital scanning?	
Is it reverse numbered?	

Order Information

Unit of Sale

- ☐ Bottle
- ☑ Box/Carton
- ☐ Ampule
- ☐ Glass
- ☐ Tube
- ☐ Vial Liquid Single
- ☐ Vial Liquid Multi
- ☐ Vial Powder Single
- ☐ Vial Powder Multi
- ☐ Other

What is NDC Selling Unit?

1 carton of 12 syringes

Minimum Order Quantity? Yes

If yes, how many of which package type?

1 Each

Inner/Carton/Pack

Case

Item and Packaging Information

	Weight LBS:	Depth	Height	Width:	Volume (Cube)	# Pieces:
Item:	0.27	3.20	6.24	2.73	54.51264	1
Box/ Carton						
Case	11	19.09	8.34	13.26	2111.132 556	36
Pallet:						

UPC: Case: 70303786961123

Carton: N/A

Wholesaler Use Only:

Vendor #

Whls. Code #:

Fineline Code:

Pharmacy Order / Bill Unit

Rec. sell unit to customer?

Rx billing unit to pharmacy:

- ☑ Each
- ☐ Gram
- ☐ Milliliter

Other Product Information

Size/Strength/Form: 12, 40 mg/mL, Injection

Product Shape: N/A

Product Color N/A

Product Imprint N/A

Cost Information

Regular Cost Per Unit of Sale ($)	Invoice Cost (WAC) ($) *	Federal Excise Tax Per Unit of
	1950	

As of Date:

Attach copy of SAFETY DATA SHEET (SDS) or non hazar letter, PACKAGE INSERT, LABEL AND PHOTO OF PRODUCT PAKCAGING and BARCODE

*Please provide any additional information on page 2. See new p. 3 for Designated Drop Ship Only. **Signature:**

KEEP REFRIGERATED (2° to 8°C/36° to 46°F) AND PROTECT FROM LIGHT.

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Policies & Procedures

Hercules Pharmaceuticals, Inc. Policies and Procedures, Section 9.3.2.1.4

"Logistics personnel shall use adequate shipping containers, pursuant to Section 9.2.1., and time-in-transit metrics to ensure products that require specific conditions stay within required parameters during shipment …"

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Heading

KoolTemp® GTS Rx 3L
+2°C to +8°C, Cold Pack-out

COLD CHAIN TECHNOLOGIES

Place Items In Order As Follows:

A. The product load (3), centered inside the base (2).

B. Temperature indicator (7) directly on top of the product. (OPTIONAL STEP)

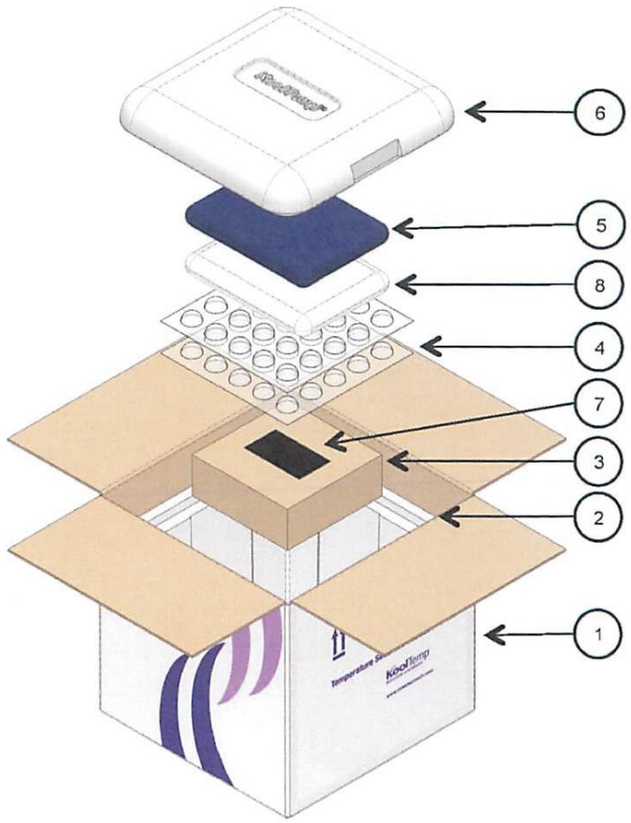
C. Two layers of bubble wrap (4) on top of the product load (3) and temperature indicator (7).

D. One refrigerated 620E gel pack (8) on top of the bubble wrap (4).

E. One frozen 620E gel pack (5) on top of the previously placed refrigerated 620E gel pack. (8).

F. Fill all void space with bubble wrap (4) (not shown).

G. Lid (6) on top of the base (2) and tape closed the outer corrugated box (1).



INITIAL REFRIGERANT CONDITIONING AT PACK OUT			
Liquid +5°C / Solid -5°C to 0°C			
Shipper components are Pre-Conditioned at Room Temperature			
	LENGTH	WIDTH	HEIGHT
SHIPPING SYSTEM O.D.	11.94" (303.27 mm)	11.94" (303.27 mm)	11.89" (302 mm)
AVAILABLE PAYLOAD SPACE	7.5" (190.5mm)	7.5" (190.5mm)	3.75" (95.25mm)
SHIPPING SYSTEM WEIGHT W/O PRODUCT LOAD	3.95 lbs. (1.79kg)		

Bill of Materials	
Item #	Qty.
KT888-CISU	1
620E	2

*Note: Removing a frozen 620E gel pack from a typical -20°C freezer & staging in a room temperature (~22°C) environment for ~30 minutes prior to pack-out will bring the frozen gel pack to the desired -5°C to 0°C .

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Ethical, Secured & Accredited Supply Chain for Biosimilars

Together, we can do things better

Hercules Rx
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Medical Device Hot Topics: New Regulatory Models in Lab Developed Tests and Digital Health

Bethany J. Hills, Esq. (Panel Chair)
Mintz Levin | New York, NY

Aaron Josephson, M.S.
ML Strategies, LLC | Washington, DC

Lesley R. Maloney
Roche Diagnostics | Washington, DC

Howard A. Zucker, M.D., JD
New York State Department of Health | Albany, NY

Charting New Courses:
FDA's Approaches to LDTs & Digital Health

New York State Bar Association Annual Meeting
January 17, 2019

Aaron Josephson
Senior Director – ML Strategies

Hot Topics in Device Regulation & Oversight

- LDTs
- Digital Health
- 510(k) Modernization
- De Novo Proposed Rule
- Progressive Approval
- Collaborative Communities
- Device Shortages
- Servicing/Remanufacturing
- Quality
- Cybersecurity

LDTs

Important Considerations

- According to FDA:
  - A laboratory developed test (LDT) is a type of in vitro diagnostic (IVD) test that is designed, manufactured and used within a single laboratory
  - The FDA does not consider diagnostic devices to be LDTs if they are designed or manufactured completely, or partly, outside of the laboratory that offers and uses them

Abbreviated History

- 1976: Medical Device Amendments to Federal Food, Drug, and Cosmetic Act included IVDs in definition of device; FDA begins exercising enforcement discretion
- 1988: CLIA gives CMS authority to regulate labs (focus on ability of lab to perform accurate and reliable testing)
- 2014: FDA draft guidance announces end to enforcement discretion for most LDTs; Congress and industry urge FDA not to finalize guidance and instead seek legislative solution
- 2017: Diagnostic Accuracy and Innovation Act (DAIA) discussion draft released
- August 2018: FDA sent “technical assistance” to Congress
- December 2018: Verifying Accurate Leading-edge IVCT Development (VALID) Act discussion draft released

DAIA & FDA Technical Assistance

DAIA

- Would create new medical product category (In Vitro Clinical Tests – IVCTs) separate from devices, drugs, biologics; would create new IVCT Center at FDA
- FDA oversight: design, development, validation, manufacturing
- Standard: reasonable assurance of analytical validity and clinical validity for intended use
- Premarket submission requirement based on risk of test; no predicates
- Quarterly summary reports of malfunctions; individual adverse event reports required for events involving death or imminent public health threat
- Would require new regulations to be promulgated
- Compliance phased-in; grandfather period for tests introduced >3 months before enactment
- FDA can withdraw tests, conduct inspections, order recalls
- User fees capped at 30% of program cost

FDA Technical Assistance

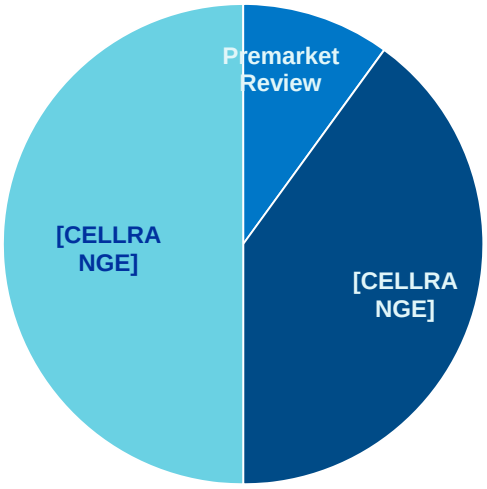
- Legislation should include authority for:
  - Precertification
  - Third Party Review
  - Collaboration
- Concerns:
  - Burdensome to create new Center
  - Automatic decisions (e.g., 60d to agree with sponsor proposed classification)
  - Grandfathered tests being out of agency's reach for enforcement even if they do not demonstrate analytical or clinical validity
  - Agency prefers transition that does not require operating two regulatory schemes simultaneously
  - User fees should be negotiated and without artificial cap

VALID Act

- Keeps definition of IVCTs
- Does not mandate creation of new Center within FDA
- Allows for precertification, Third Party Review, and Collaborative Communities
- Grandfathered tests must be labeled to indicate their grandfather status; developers must meet other criteria
- Gives FDA authority to request information about any IVCT that FDA believes may not be analytically or clinically valid, does not perform as intended, or presents a safety issue
  - FDA can order the developer cease distribution and/or order a recall
- Allows "mitigating measures"
- Requires FDA to develop recommendations for a user fee program
  - Must consult with Congress, health care providers, patient and consumer advocacy groups, regulated industry

Precertification for LDT Developers

- No premarket review if IVCT developer is precertified
- Precertification based on:
  - Methods, facilities, and controls used to develop IVCTs conform with QS requirements
  - How procedures for analytical and clinical validation provide a reasonable assurance of such
  - Raw data for one of each type of IVCT developed by the developer



Third Party Review

- Would apply to review of applications for precertification, applications for premarket approval, and inspections
- Mirrors existing Third Party Review scheme for 510(k)s
- FDA website lists all third party reviewers and performance data
- Allows FDA to leverage trusted entities, saving time and resources
- Example of third party review paradigm – New York State Department of Health (NYSDOH)

Risk category	Submission	Initial Approval	Review	Review Priority
High	Yes	None	Yes	High
Moderate	Yes	Conditional[1,2]	Yes	Medium
Low	Yes	Full[1,2]	No[3]	n/a

[1] Provided the laboratory holds the appropriate permit category.
[2] The Department reserves the right to withhold approval at its discretion.
[3] The Department reserves the right to review all applications at its discretion.

Politics

- House Energy & Commerce Committee – new leadership
  - Rep. Frank Pallone (D-NJ) chairman
  - Rep. Anna Eshoo (D-CA) likely chair of health subcommittee; Medtech Caucus, critical of safety issues
  - Democrats generally not fans of: precertification, third party review
- Senate Health, Education, Labor, and Pensions (HELP) Committee – same leadership
  - Sen. Lamar Alexander (R-TN); Sen. Patty Murray (D-WA)
- Generally:
  - Republicans concerned about regulation limiting patient access and innovation
  - Democrats concerned about accurate tests

Digital Health: New Paradigm

Current framework

- Regulation of product
- New products/product versions may trigger FDA premarket review requirements
- Quality system evaluated in postmarket inspections

Proposed framework

- Regulation of product developer
- Streamlined or no review of new products/product versions
- Premarket excellence appraisal

Digital Health Precertification

- Problem: no expertise or capacity at FDA to review complex digital health technologies, including software; FDA says software does not fit in existing regulatory model due to fast development/iteration cycles
- Solution: Precertify developers based on **culture of quality and organizational excellence**
- Scope: any organization that intends to develop or market regulated software in the U.S.
- Four components of the new program
  - Excellence Appraisal and Precertification
  - Review Pathway Determination
  - Streamlined Premarket Review Process
  - Real World Performance

Excellence Appraisal and Precertification

- 5 Excellence Principles to be evaluated (proposed):
  - Product Quality
  - Patient Safety
  - Clinical Responsibility
  - Cybersecurity Responsibility
  - Proactive Culture

Review Pathway Determination

- Premarket review based on:
  - Precertification status
  - Precertification level
    - Level 1: low-risk devices generally marketed by companies with little or no experience
    - Level 2: low- and moderate-risk devices generally marketed by companies with a proven track record
  - Device risk, which accounts for:
    - Significance of the information provided by the device (software) to the health care decision
    - State of health
    - Software function

Streamlined Premarket Review Process

- Understand the product
  - FDA works with developer iteratively to understand details of software functions
  - How: Interactive demonstration? Submission of software wireframe?
- Premarket review
  - Analytical performance, clinical performance, safety measures
  - How: Screen sharing, access to development environment, testing logs?
- Marketing authorization
  - Decision made, documented, and communicated

Real World Performance

- FDA: excellent organizations consistently collect and analyze post-launch data from diverse sources to inform their operations and decision making, from quality control to product development for new market segments
- Real World Performance Analytics: systematic computational analyses of all data relevant to the safety, effectiveness, and performance of marketed software
  - Real World Health Analytics; e.g., human factors/usability, clinical safety, health benefits
  - User Experience Analytics; e.g., user satisfaction, issue resolution, user engagement
  - Product Performance Analytics; e.g., cybersecurity, product performance

Risks

- Heavy reliance on postmarket monitoring to identify trouble spots but immature postmarket data collection and surveillance apparatus
- Patient confidence
- Liability
- Political
  - October 10, 2018 letter to FDA from Sens. Warren, Murray, and Smith with questions about:
    - Legal authority
    - Data requirements to demonstrate excellence
    - Third parties conducting pre-cert assessments
    - FDA postmarket oversight of software (e.g., inspections)

Discussion

FDA's views on the Diagnostic Accuracy and Innovation Act (DAIA)

These comments are intended only to provide technical assistance and are by no means to be interpreted as any kind of approval or endorsement of the legislation by the Department of Health and Human Services and its agencies or the Administration.

The FDA supports the goal of legislation to create a predictable path to market for all in vitro clinical tests (IVCTs) that is a risk-based approach consistent with the least burdensome principle for regulation and assuring necessary safeguards for consumers.

Patients and health care providers need accurate, reliable, and clinically valid tests to make good health care decisions. Inaccurate or false test results, or accurate measurements with an invalid claim regarding the test results' relationship to a disease, can lead to patient harm. While excessive oversight can discourage innovation, inadequate and inconsistent oversight in which different test developers are treated differently can also discourage innovation by making it difficult for high-quality test developers to compete with poorer performing counterparts.

To achieve this goal, FDA believes it is necessary to create pathways that are efficient and achieve reasonable assurance of analytical and clinical validity, without imposing unnecessary burdens.

SECTION. 1. SHORT TITLE;

TABLE OF CONTENTS

(a) This Act may be cited as the _____.
(b) Table of Contents. — The table of contents of this Act is as follows:

SEC. 2. DEFINITION.

(a) Section 201 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. § 321) is amended—

(1) by adding at the end the following:

"(ss)

"(1) The term 'in vitro clinical test' means—

"(A) a test intended to be used in the collection, preparation, analysis, or in vitro clinical examination of specimens taken or derived from the human body for the purpose of

"(i) identifying, diagnosing, screening, measuring, detecting, predicting, prognosing, analyzing, or monitoring a disease or condition, including a determination of the state of health; or

"(ii) selecting, monitoring, or informing therapy or treatment for a disease or condition;

"(B) a test protocol for a use described in subparagraph (A);

"(C) a test platform for use in or with a test described in subparagraph (A);

"(D) an article for taking or deriving specimens from the human body for a purpose described in subparagraph (A);

"(E) software for a purpose described in subparagraph (A), excluding software specified under section 520(o) as not within the definition a device under this Act; or

"(F) subject to paragraph (2), a component, part, or accessory of a test described in this paragraph, whether alone or in combination, including but not limited to reagents, calibrators, and controls.

"(2) Notwithstanding paragraph (1), the following articles, if intended to be used as components, parts, or accessories of an in vitro clinical test, are not in vitro clinical tests:

"(A) Blood, blood components, and human cells or tissues, from the time of donation or recovery of such article, including determination of donor eligibility, as applicable, until such time as the article is released into interstate commerce as a component, part, or accessory of an in vitro clinical test by the establishment that collected such article;

"(B) Articles used for invasive sampling;

"(C) General purpose laboratory equipment; and

"(D) Articles used solely for personal protection during the administering, conducting, or otherwise performing test activities.

(2) by adding at the end of subsection (g) the following:

"(3) The term 'drug' does not include an in vitro clinical test as defined in this section."; and

(3) in subsection (h), by striking "section 520520(o)" and inserting the following:

"section 520(o) or an in vitro clinical test as defined in subsection(ss).".

(b) Section 351 of the Public Health Service Act (42 U.S.C. § 262) is amended by adding at the end of subsection (i)(1) the following:

"The term 'biological product' does not include an in vitro clinical test as defined in section 201(ss) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. § 321(ss))."

SEC. 3. REGULATION OF IN VITRO CLINICAL TESTS.

The Federal Food, Drug, and Cosmetic Act (21 U.S.C. § 301 et seq.) is amended—

(a) by amending the title of Chapter V to read as follows "Drugs, Devices, and In Vitro Clinical Tests"; and

(b) by adding at the end of Chapter V the following:

"Subchapter J—In Vitro Clinical Tests

"SEC. 587. DEFINITIONS.

"In this part—

"(1) ANALYTICAL VALIDITY The term 'analytical validity' means, the ability of an in vitro clinical test to adequately identify, measure or detect a target analyte or substance that such test is intended to identify, measure, or detect. For articles for taking or deriving specimens from the human body under section 201(ss)(1)(DD) of this Act, analytical validity means a reasonable assurance that such article performs as intended and, will support the analytical validity of tests with which it is used.,.

"(2) CLINICAL USE. The term 'clinical use' means the operation, application, or functioning of an in vitro clinical test in connection with human specimens, including

patient, consumer, and donor specimens, for the purposes specified in section 201(ss)(1)(A).

"(3) CLINICAL VALIDITY. The term 'clinical validity' means the ability of an in vitro clinical test to adequately achieve the purpose for which it is intended as described under section 201(ss)(1)(A).

"(4) COMPREHENSIVE TEST INFORMATION SYSTEM. The term 'comprehensive test information system' means an on-line database that the Secretary may use to store and provide information about in vitro clinical tests to developers and the general public, as described in section [CTIS].

"(5) CROSS-REFERENCED TEST. The term 'cross-referenced test' means an in vitro clinical test that –

> "(A) references in its labeling the trade name or intended use of another medical product that is not an in vitro clinical test; or
>
> "(B)is referenced by trade name or intended use in the labeling of another medical product that is not an in vitro clinical test.

"(6) DEVELOPER. The term 'developer' means a person who—

> "(A) develops an in vitro clinical test, including by designing, validating, producing, manufacturing, remanufacturing, propagating, or assembling the kit of an in vitro clinical test,
>
> "(B) imports an in vitro clinical test, or
>
> "(C) modifies an in vitro clinical test initially developed by a different person in a manner that changes any of the notification elements specified in paragraph (12) that define a test group, performance claims, or, as applicable, safety of such in vitro clinical test, or adversely affects performance of the in vitro clinical test.

"(7) HIGH RISK. The term 'high-risk', with respect to an in vitro clinical test or category of in vitro clinical tests, means that—

> "(A)subject to subparagraph (B), an undetected inaccurate result from such in vitro clinical test, or such category of in vitro clinical tests----
>
> > "(i) when used as intended, would likely cause serious or irreversible harm or death to a patient or patients, or would otherwise cause serious harm to the public health; and
> >
> > "(ii) the likelihood of adverse patient impact or adverse public health impact caused by such an inaccurate result is not remote.
>
> "(B) An in vitro clinical test is not a high risk in vitro clinical test if mitigating measures are established and applied to sufficiently mitigate the risk of inaccurate results as described in subparagraph (A), taking into account—

"(i) the degree to which the technology for the intended use of the in vitro clinical test is well characterized, and the criteria for performance are well established to be sufficient for the intended use; and

"(ii) the clinical circumstances (including clinical presentation) under which the in vitro clinical test is used, and the availability of other tests (such as confirmatory or adjunctive tests) or relevant material standards.

"(8) IN VITRO CLINICAL TEST. The term "in vitro clinical test' has the meaning set forth in section 201(ss).

"(9) LOW-RISK. The term 'low-risk', with respect to an in vitro clinical test or category of in vitro clinical tests, means that an undetected inaccurate result from such in vitro clinical test, or such category of in vitro clinical tests, when used as intended—

"(A) would cause minimal or no harm or disability, or immediately reversible harm, or would lead to only a remote risk of adverse patient impact or adverse public health impact; or

"(B) (i) could cause non-life threatening injury or injury that is medically reversible, or delay necessary treatment; and

"(ii) mitigating measures are sufficient to prevent such inaccurate result, detect such inaccurate result prior to any adverse patient impact or adverse public health impact, or otherwise sufficiently mitigate the risk associated with such inaccurate result.

"(10) MITIGATING MEASURES. The term 'mitigating measures' ---

"(A) means requirements that the Secretary determines, based on available evidence, are necessary ---

"(i) for an in vitro clinical test, or a category of in vitro clinical tests, to meet the relevant standard for its intended use as defined in paragraph (11), or

"(ii) to mitigate the risk of harm ensuing from a false result or misinterpretation of any result; and

"(B) includes applicable requirements regarding labeling, advertising, website posting of information, testing, clinical studies, postmarket surveillance, user comprehension studies, training, conformance to standards, and performance criteria.

(11**)** RELEVANT STANDARD. The term 'relevant standard', with respect to an in vitro clinical test, means a reasonable assurance of analytical and clinical validity, except that such term —

"(A)with respect to provisional approval under [Section X], means a reasonable assurance of analytical validity and probable clinical validity;

"(B)with respect to test platforms as defined in [Section X], means a reasonable assurance of analytical validity; and

"(C)with respect to articles for taking or deriving specimens from the human body for purposes described in section 201(ss)(1)(A)(i) or (ii) as defined by [Section

X], means a reasonable assurance of analytical validity and, where applicable, safety.

"(12) TEST GROUP. The term 'test group' means one or more tests that have the following notification elements in common—

"(A) substance or substances measured by the in vitro clinical test, such as analyte, protein, or pathogen;

"(B) type or types of specimen or sample;

"(C) test method;

"(D) test purpose, as described in section 201(ss)(1)(A), such as screening, predicting, or monitoring;

"(E) disease or condition for which the in vitro clinical test is intended for use;

"(F) intended patient population; and

"(G) context of use, such as in a clinical laboratory, in a health care facility, prescription home use, over-the-counter use, or direct-to-consumer testing.

"(13) TEST PLATFORM. The term 'test platform' means hardware, including software used to effectuate the hardware's functionality, intended to be used with other in vitro clinical tests in the generation of a test result.

"(14) VALID SCIENTIFIC EVIDENCE. The term 'valid scientific evidence' means evidence from which it can fairly and responsibly be concluded by qualified experts that the relevant standard has been met for an in vitro clinical test for its intended use, including (depending on the characteristics of the in vitro clinical test, its intended use, the existence and adequacy of warnings and other restrictions, and the extent and nature of clinical experience relevant to its use) ---.

"(A) clinical studies;

"(B) evidence or data from peer-reviewed literature;

"(C) reports of significant human experience with an in vitro clinical test;

"(D) bench studies, well-documented case studies or case histories conducted by qualified experts;

"(E) clinical data, data registries, or postmarket data;

"(F) data collected in countries other than the United States if such data are demonstrated to be adequate for the purpose of making a regulatory determination under the relevant standard in the United States; and

"(G) where appropriate, clinical practice guidelines, consensus standards and reference standards.

"(15) FIRST-OF-A-KIND. The term 'first-of-a-kind' means an in vitro clinical test that has a combination of the notification elements under paragraph (12) that makes up a test group that differs from the combination in any legally available test group.

"(16) WELL-CHARACTERIZED. The term 'well-characterized' means well-established and well-recognized by the scientific or clinical community, if adequately evidenced by one or more of the following:

"(A) Literature;

"(B) Practice guidelines;

"(C) Consensus standards;

"(D) Recognized standards of care;

"(E) Technology in use for many years;

"(F) Scientific publication by multiple sites;

"(G) Wide recognition or adoption by the scientific or clinical community; and

"(H) Real world data."

"SEC. 587A. APPLICABILITY.

"(a) IN GENERAL. —

"(1) SCOPE. An in vitro clinical test –

"(A) shall be subject to the requirements of this subchapter, except as set forth in this section;

"(B) that is offered for clinical use is deemed to be introduced into interstate commerce for purposes of enforcing the requirements of this Act; and

"(C) subject to any exemption or exclusion in this section, shall not be subject to any provision or requirement of this Act other than this subchapter unless such other provision or requirement—

"(i) applies expressly to in vitro clinical tests; or

"(ii) applies with respect to –

"(I) all articles regulated by the Secretary through the Food and Drug Administration;

"(II) a subset of such articles that includes in vitro clinical tests; or

"(iii) describes the authority of the Secretary when regulating such articles or subset of articles.

"(2) LABORATORIES AND BLOOD AND TISSUE ESTABLISHMENTS.

"(A) Nothing in this subchapter shall be construed to change or modify the authority of the Secretary with respect to laboratories or clinical laboratories under section 353 of the Public Health Service Act, or any regulations promulgated thereunder.

"(B) In implementing this subchapter, the Secretary shall, to the greatest extent possible, unless necessary to protect public health, avoid undertaking programmatic regulatory functions separately being undertaken by the Secretary under section 353 of the Public Health Service Act, or any regulations promulgated thereunder.

"(C) Nothing in this subchapter shall be construed to change or modify the authority of the Secretary with respect to laboratories, establishments or other facilities engaged in the propagation, manufacture, or preparation, including but not limited to filling, testing, labelling, packaging, and storage, of blood, blood components, human cells, tissues or tissue products under this Act or Section 351 of the Public Health Service Act.

"(3) PRACTICE OF MEDICINE. —

"(A) Nothing in this subchapter shall be construed to limit or interfere with the authority of a health care practitioner to prescribe or administer any legally marketed in vitro clinical test for any condition or disease within a legitimate health care practitioner-patient relationship.

"(B) This paragraph shall not limit any authority of the Secretary to establish and enforce restrictions on the sale or distribution, or in the labeling, of an in vitro clinical test that are part of a determination of precertification, established as a condition of approval, or promulgated through regulations or otherwise.

"(C) This section shall not be construed to alter any prohibition on the promotion of unapproved uses of legally marketed in vitro clinical tests.

"(4) SPECIAL RULE. —

"(A) Notwithstanding the exemptions from premarket review set forth in subsections (b), (c), (d), (e), (f), (g), (h), and (k) of this section, an in vitro clinical test shall be subject to the requirements of section [premarket review] if the Secretary determines, in accordance with subparagraph (B), that—

"(i) there is insufficient valid scientific evidence that an article for taking or deriving specimens from the human body for the purposes specified in section 201(ss) performs as intended, will support the analytical validity of tests with which it is used, or, where applicable, is safe for use

"(ii)there is insufficient valid scientific evidence to support the analytical validity or the clinical validity of such in vitro clinical test;

"(iii)such in vitro clinical test is being offered by its developer with materially deceptive or fraudulent analytical or clinical claims; or

"(iv)there is a reasonable potential that such in vitro clinical test will cause death or serious adverse health consequences, including by causing the absence, delay, or discontinuation of appropriate medical treatment.

"(B) PROCESS. —

"(i) If the Secretary has reason to believe that one or more of the criteria set forth in subparagraph (A) apply to an in vitro clinical test, the Secretary may request the developer to submit information pertaining to such criteria and to establishing the basis for any claimed exemption from premarket review.

"(ii) Upon receiving a request for information under subparagraph (B)(i), the developer shall submit the information within 30 days of the request.

"(iii) The Secretary shall review the information submitted within 30 days of its receipt. If the Secretary makes one or more of the findings specified in subparagraph (A), the developer shall promptly submit an application for premarket review, which submission shall be made no later than 90 days from such finding.

"(iv) If an application for premarket review is pending in accordance with clause (iii), the in vitro clinical test may continue to be marketed for clinical use while the application is pending, unless the Secretary issues an order to the developer to immediately cease distribution of the test in the best interest of the public health, which order may also direct the developer to immediately notify health professionals and other user facilities to cease use of such in vitro clinical test.

"(v) If the developer fails to submit an application for premarket review of a test as required under clause (iii), or if the Secretary determines not to approve an application submitted under this paragraph, the Secretary may issue an order as described in clause (vi).

"(vi) If the Secretary makes one of the findings specified in subparagraph (A) with respect to an in vitro clinical test, the Secretary may issue an order requiring the developer of such in vitro clinical test, and any other appropriate person (including a distributor or retailer of the in vitro clinical test)—

"(I) to immediately cease distribution of such in vitro clinical test pending approval of an application under section [587B - premarket review]; and

"(II) to immediately notify health professionals and other user facilities of the order and to instruct such professionals and facilities to cease use of such in vitro clinical test.

Such order shall provide the person subject to the order with an opportunity for an informal hearing, to be held not later than 10 days after the date of the issuance of the order, on the actions required by the order and on whether the order should be amended to require a recall of such in vitro clinical test. If, after providing an opportunity for such a hearing, the Secretary determines that inadequate grounds exist to support the actions required by the order, the Secretary shall vacate the order.

"(vii) If the Secretary determines that an order issued under clause (vi) should be amended to include a recall of the in vitro clinical test with respect to which the order was issued, the Secretary shall amend the order to require a recall. The Secretary shall specify a timetable in which the in vitro clinical test

recall will occur and shall require periodic reports to the Secretary describing the progress of the recall.

"(viii) Any order issued under this paragraph with respect to an in vitro clinical test shall cease to be in effect if such test is granted approval under sections [premarket review, provisional approval], provided that the in vitro clinical test is developed and offered for clinical use in accordance with such approval.

"(5) EMERGENCY USE.–

"(A) IN GENERAL.—The exemptions set forth in this section shall not apply to any in vitro clinical test that is eligible for an emergency use authorization under section 564.

"(B) TESTS OFFERED FOR CLINICAL USE UNDER AN EXEMPTION PRIOR TO A DECLARATION.—

"(i) (I) Subject to subclause (II), an in vitro clinical test that would be eligible for an emergency use authorization under section 564 that is offered for clinical use under an exemption in [APPLICABILITY SECTION] prior to a declaration under section 564(b) affecting such test may continue to be offered for clinical use after such declaration only after it has been approved under section [premarket review] or granted an emergency use authorization under section 564.

"(II) However, if an application for approval is submitted under section [premarket review, (b)] or a request for emergency use authorization is submitted under section 564 not later than [5] days after a declaration, such test described in subclause (I) may be offered for clinical use until the application or request is denied.

"(ii) The Secretary, in collaboration with the developer and other affected entities, as appropriate, shall take necessary actions to ensure such tests are no longer distributed or offered for clinical use until they receive the required approval or authorization.

"(b) COMPONENTS, PARTS, AND ACCESSORIES. —

"(1) EXEMPTION. —

"(A) Subject to paragraph (b), an in vitro clinical test that is a component, part, or accessory within the meaning of section 201(ss)(1)(E), is exempt from the requirements of this subchapter and this Act, subject to the limitation described in subparagraph (B), if it is intended for further development under paragraph (2). Test platforms, articles for taking or deriving specimens from the human body, and software, as defined by subparagraphs (B) through (D) of section 201(ss)(1) are not considered to be components, parts, or accessories and are not eligible for this exemption.

"(B) Notwithstanding subparagraph (A), an in vitro clinical test that uses a component, part, or accessory described in such subparagraph shall be subject to

the requirements of this subchapter and this Act, including requirements relating to the establishment and use of supplier controls, unless such in vitro clinical test is otherwise exempted under this section.

"(2) FURTHER DEVELOPMENT. — An in vitro clinical test that is a component, part, or accessory as described in paragraph (1) intended for further development if—

"(A) it is intended solely for use in the development of another in vitro clinical test and

"(B) if introduced or delivered for introduction into interstate commerce after the date of enactment of this [subchapter/bill name], the labeling of such in vitro clinical test bears the following statement: "This product is intended solely for further development of an in vitro clinical test and is exempt from FDA regulation. This product must be evaluated by the in vitro clinical test developer in accordance with supplier controls if it is used with or in the development of an in vitro clinical test."

"(c) GRANDFATHERED TESTS. —

"(1) EXEMPTION. — An in vitro clinical test that meets the criteria set forth in paragraph (2) is exempt from premarket review under section [x], the labeling requirements under section [x], and the quality system requirements under section [x], and may be lawfully marketed subject to the other requirements of this subchapter and other applicable requirements of this Act, if—

"(A) Each test report template under section [LABELING] bears a statement of adequate prominence that reads as follows "This in vitro clinical test was developed and first introduced prior to [90 days prior to date of bill enactment] and has not been reviewed by the Food and Drug Administration"; and

"(B) The developer of such in vitro clinical test maintains documentation demonstrating that such test meets and continues to meet the criteria set forth in paragraph (2), which documentation shall be available to the Secretary upon request.

"(2) CRITERIA FOR EXEMPTION. — An in vitro clinical test is exempt as specified in paragraph (1) if it–

"(A) was developed by a laboratory certified by the Secretary under section 263a of title 42 that meets the requirements for performing high-complexity testing for use only within that certified laboratory and was first offered for clinical use or otherwise introduced or delivered for introduction into interstate commerce by that laboratory 90 days or more before the date of enactment of [subchapter/bill];]

"(B) does not have an approval under section 515, a clearance under section 510(k), an authorization under 513(f)(2), or an approval under 520(m);

"(C) is not modified on or after the date that is 90 days before the date of enactment of this [bill/subchapter] by its initial developer (or another person) in a manner such that it is a new in vitro clinical test according to [section l(1) (Modified Tests)]."(3) (A) When a person modifies its own or another person's in vitro clinical test that is exempt under

this subsection and makes a determination that it is not a new in vitro clinical test according to section l(1) [(Modified Tests)],section l(1) [(Modified Tests)], the person must document the modification(s) and basis for such determination and provide it to the Secretary upon request or inspection.

"(d) TESTS EXEMPT FROM 510(k) [PRIOR TO ENACTMENT OF [SUBCHAPTER/BILLNAME] —

"(1) EXEMPTION. — An in vitro clinical test is exempt from the requirements of section [premarket review], and may be lawfully marketed subject to the other requirements of this subchapter and other applicable requirements of this Act, if it meets the criteria for exemption described in paragraph 2.

"(2) CRITERIA FOR EXEMPTION. — An in vitro clinical test is exempt from the requirements of section [premarket review] if—

"(A) such test was offered for clinical use prior to the effective date of this [subchapter/bill], and was exempt from submission of a report under section 510(k) of the Act [21 U.S.C. 360(k)] pursuant to [the FDCA] (including class II 510(k)-exempt devices and excluding class I reserved devices); or

"(B) such test was not offered for clinical use prior to the effective date of this [subchapter/bill name] and—

"(i) is not a test platform as defined in [DEFINITIONS]; and

"(ii) falls within a category of tests that was exempt from submission of a report under section 510(k) [21 U.S.C. 360(k)] prior to the effective date of this [subchapter/bill name] (including class II 510(k)-exempt devices and excluding class I reserved devices).

"(3) EFFECT ON SPECIAL CONTROLS.—For any in vitro clinical test, or category of in vitro clinical tests, that is exempted from premarket review based on the criteria in paragraph (2), any special control that applied to a device within a predecessor category immediately prior to the date of enactment of this subsection shall be deemed a mitigating measure applicable to an in vitro clinical test within the successor category, , except to the extent such mitigating measure is withdrawn or changed in accordance with section [mitigating measures].

"(e) LOW-RISK TESTS. —

"(1) EXEMPTION. — An in vitro clinical test is exempt from the requirements of section [premarket review], and may be lawfully marketed subject to the other requirements of this subchapter and other applicable requirements of this Act, if such test is listed, or falls within a category of tests that is listed, as a low-risk test in the list that the Secretary maintains on the website of the Food and Drug Administration pursuant to paragraph (2).

"(2) LIST OF LOW-RISK TESTS.

"(A) The Secretary shall maintain, on the website of the Food and Drug Administration, a list of in vitro clinical tests, or categories of in vitro clinical tests, that have been designated as low-risk in accordance with this paragraph.

"(B) The list required under this paragraph shall include all tests or categories of tests that meet the criteria under subsection (d) for tests exempt from section 510(k) (including class II exempt devices and excluding class I reserved devices).

"(C) Notwithstanding subchapter II of chapter 5 of title 5, the Secretary may designate an additional in vitro clinical test, or category of in vitro clinical tests, as low-risk by adding it to the list required under this paragraph upon the initiative of the Secretary or in response to a request by any person. In determining whether an additional in vitro clinical test, or category of in vitro clinical tests, should be designated as low-risk, the Secretary shall consider—

"(i) whether such test, or category of tests, meets the definition of 'low-risk' set forth in section [x]; and

"(ii) such other factors as the Secretary may deem relevant.

"(f) MANUAL TESTS. —

"(1) EXEMPTION. — An in vitro clinical test that is designed, manufactured, and used within a single laboratory certified by the Secretary under section 263a of title 42 that meets the requirements for performing high-complexity testing is exempt from the requirements of this subchapter and this Act, if

"(A) it meets the criteria for exemption described in paragraph (2); and

"(B) it is not intended—

"(i)for detecting HIV, or for measuring an analyte that serves as a surrogate marker for screening, diagnosis, or monitoring or monitoring therapy for acquired immune deficiency syndrome (AIDS);

"(ii) for testing donors, donations, and recipients of blood, blood components, human cells, tissues, cellular-based products, or tissue-based products; or

"(iii)for testing maternal or fetal specimens in determining hemolytic disease of the fetus and newborn.]

"(2) CRITERIA FOR EXEMPTION. — An in vitro clinical test is exempt as specified in paragraph (1) if its output is the result of manual interpretation (meaning direct observation) by a qualified laboratory professional, without the use of automated instrumentation or software for intermediate or final interpretation, and is either

"(A) not a high-risk test; or

"(B) a high-risk test that the Secretary determines through issuance of a notice in the Federal Register is appropriate to be exempted and that meets one of the following conditions—

"(i) no component, part, or accessory of such test, including any reagent, is introduced into interstate commerce under the exemption for tests intended for further development under subsection (b)(1), and the article for taking or deriving specimens from the human body complies with the requirements of this Act; or

"(ii) the test has been developed in accordance with Section 587I [QS, supplier controls].

"(g) TESTS FOR RARE DISEASES. —

"(1) EXEMPTION — An in vitro clinical test is exempt from premarket review under section [x], and may be lawfully marketed subject to the other requirements of this subchapter and other applicable requirements of this Act, if—

"(A) it meets the criteria for exemption under paragraph (2); and

"(B) The developer maintains documentation demonstrating that such test meets and continues to meet the criteria set forth in paragraph (2), which documentation—

"(i) shall be available to the Secretary upon request; and

"(ii) may include literature citations in specialized medical journals, textbooks, specialized medical society proceedings, governmental statistics publications, or, if no such studies or literature citations exist, credible conclusions from appropriate research or surveys.

"(2) CRITERION FOR EXEMPTION. The criteria for the exemption under this subsection from premarket review are—

"(A) fewer than 8,000 individuals per year in the United States would be subject to testing using such in vitro clinical test;

"(B) such in vitro clinical test is not cross-referenced; and

"(C) such in vitro clinical test is not for a communicable disease

"(h) CUSTOM TESTS AND LOW-VOLUME TESTS. —

"(1) EXEMPTION. — An in vitro clinical test is exempt from premarket review under section [x], the quality system requirements under section [x], and the notification requirement in section [x], and may be lawfully marketed subject to the other requirements of this subchapter and other applicable requirements of this Act, if –

"(A) The developer maintains documentation demonstrating that such test meets and continues to meet the applicable criteria set forth in paragraph (2), which documentation shall be available to the Secretary upon request; and

"(B) The developer informs the Secretary, on an annual basis, in a manner prescribed by the Secretary in Level 2 guidance, that such in vitro clinical test was introduced into interstate commerce.

"(2) CRITERIA FOR EXEMPTION. — An in vitro clinical test is exempt under paragraph (1) if—

"(A) It is not included in a test menu, template test report, or other promotional materials, and is not otherwise advertised;

"(B) It is developed or modified in order to comply with the order of an individual physician, dentist, or other health care professional (or any other specially qualified person designated under regulations promulgated by the Secretary); and

"(C) It is either

"(i) a custom test to diagnose a unique pathology or physical condition of a specific patient named in the order for which no other in vitro clinical test is commercially available in the United States, and is not used for other patients; or

"(ii) a low-volume test offered to no more than 5 patients per year.

"(i) PUBLIC HEALTH SURVEILLANCE. —

"(1) EXEMPTION. — An in vitro clinical test that is intended solely for use by a public health laboratory in public health surveillance, as described in paragraph (2), is exempt from the requirements of this subchapter and this Act.

"(2) CRITERIA FOR EXEMPTION. — An in vitro clinical test is intended solely for use in public health surveillance under paragraph (1) if it is intended solely for use on systematically collected samples for analysis and interpretation of health data essential to the planning, implementation and evaluation of public health practice, where such practice is closely integrated with the dissemination of these data to public health officials and linked to the prevention or control of disease or other public health threat. An in vitro clinical test that is either intended for use in making clinical decisions for individual patients or other purposes not described in the preceding sentence or whose individually identifiable results may be reported back to an individual patient or the patient's healthcare provider, even if also intended for public health surveillance, is not intended solely for use in public health surveillance under paragraph (1).

"(j) LAW ENFORCEMENT. — An in vitro clinical test that is intended solely for use in forensic analysis or other law enforcement activity is exempt from the requirements of this subchapter and this Act. An in vitro clinical test that is intended for use in making clinical decisions for individual patients or other purposes not described in the preceding sentence, or whose individually identifiable results may be reported back to an individual patient or the patient's healthcare provider, even if also intended for law enforcement purposes, is not intended solely for use in law enforcement under this subsection.

"(k) PRECERTIFIED TESTS. — An in vitro clinical test that is precertified under section [precertification] is exempt from the requirements of section [premarket review].

"(l) MODIFIED TESTS.–

"(1) An in vitro clinical test that is modified, by the initial developer or a different person, is a new in vitro clinical test subject to all applicable provisions of sections XXX – XXX [IVCT sections of FDCA] if the modification—

"(A) changes any of the elements specified in section 587(12) that define a test group,

"(B) changes performance claims made with respect to such in vitro clinical test;

"(C) causes an in vitro clinical test to no longer comply with applicable mitigating measures or restrictions;

"(D) adversely affects performance of the in vitro clinical test; or

"(E) as applicable, affects the safety of an article for taking or deriving specimens from the human body for a purpose described in section 201(ss).

"(2) When a person modifies an in vitro clinical test that was developed by another person, such modified test is exempt from the requirements of this subchapter and this Act provided that such person shall document the modification that was made and the basis for determining that the modification, considering the changes individually and collectively, was not a type of modification described in paragraph (1) and shall provide such documentation to the Secretary upon request or inspection.

"(m) INVESTIGATIONAL USE.——An in vitro clinical test for investigational use is exempt from the requirements of this subchapter and this Act other than the requirements of and under section [investigational use], and may be lawfully marketed subject to such requirements.

"(n) GENERAL EXEMPTION AUTHORITY.——The Secretary may, by order published in the Federal Register following notice and an opportunity for comment, exempt a class of persons from any section under this subchapter upon a finding that such exemption is appropriate in light of public health and other relevant considerations.

"(o) REGULATIONS.- The Secretary is authorized to issue regulations to implement this subchapter.

"SEC. 587B. PREMARKET REVIEW

"(a) GENERAL REQUIREMENT. — No person shall introduce or deliver for introduction into interstate commerce any in vitro clinical test, unless an approval of an application filed pursuant to subsection (b), including an approval under section [587C – priority review/provisional approval] is effective with respect to such in vitro clinical test or such in vitro clinical test is exempt from the requirements of this section under section [587A – applicability].

"(b) APPLICATION FOR PREMARKET APPROVAL. —

"(1) Any person may file with the Secretary an application for premarket approval for an in vitro clinical test.

"(2) An application submitted under paragraph (1) shall include—

"(A) The information required in 21 CFR 814. 20(a), (b)(1), (2), (3)(iii), (iv), (v), (vi), (8), (10), (12), which shall be interpreted to apply to in vitro clinical tests, until such time as regulations requiring comparable information are in effect with respect to in vitro clinical tests, at which time an application submitted under paragraph (1) shall include the information required under such regulations;

"(B) General information regarding the test, including a description of its intended use; an explanation regarding how the test functions and significant performance characteristics; a risk assessment of the test; and a statement attesting to the truthfulness and accuracy of the information submitted in the application;

"(C) Except for test platforms, information regarding the methods used in, or the facilities or controls used for, the development of the test to demonstrate compliance with the applicable quality system requirements set forth in section [QS].

"(D) Information demonstrating compliance with any applicable standards established or recognized under section [standards], or established or recognized under section 514 [prior to the date of enactment of this [subchapter/bill name], and any applicable mitigating measures established under section [mitigating measures].

"(E) Valid scientific evidence from nonclinical laboratory studies involving the test, or in the case of a test platform or article for taking or deriving specimens from the human body, with a representative test or tests covering all intended test methodologies that include the test platform or collection article, to support analytical and clinical validity, which shall include—

"(i) summary information for all supporting validation studies performed and a statement that studies were conducted in compliance with applicable good laboratory practices under part 58 of title 21 of the Code of Federal Regulations which shall be interpreted to apply to in vitro clinical tests; and

"(ii) raw data for tests that are high-risk, cross-referenced, or first-of-a-kind, unless the Secretary determines otherwise; with raw data for all other tests available upon the Secretary's request;

"(F) For in vitro clinical tests for which clinical validity is included in the relevant standard, valid scientific evidence from clinical investigations with the test involving human subjects to support clinical validity, which shall include—

"(i) raw data for tests that are high-risk, cross-referenced, or first-of-a-kind, unless the Secretary determines otherwise; with raw data for all other tests available upon the Secretary's request;

"(ii) information on clinical investigations involving human subjects including statements that any clinical investigation involving human subjects was conducted in compliance with: (I) institutional review board regulations in 21 CFR part 56, which shall be interpreted to apply to in vitro clinical tests, (II) informed consent regulations in 21 CFR part 50, which shall be interpreted to apply to in vitro clinical tests, and (III) investigational use requirements in section [investigational use], as applicable;

"(G) To the extent the application seeks authorization to make modifications within the scope of the approval, a change protocol that includes validation procedures and acceptance criteria for specific types of anticipated modifications that could be made to the test under an approved application;

"(H) For an article for taking or deriving specimens from the human body, and for any in vitro clinical test that includes such article, safety information, as applicable, including but not limited to biocompatibility, sterility, human factors studies and user studies, and information regarding the types of tests that could be used with the article;

"(I) For a test platform, and for any in vitro clinical test that includes a test platform, data, as applicable, to support software validation, electromagnetic compatibility, and electrical safety, or information demonstrating compliance with applicable recognized standards addressing these areas;

"(J) Proposed labeling, in accordance with the requirements in section [labeling]; and

"(K) Such other information as the Secretary may require through guidance.

"(3) Upon receipt of an application meeting the requirements set forth in paragraph (2), the Secretary –

"(A) may on the Secretary's own initiative, or

"(B) may, upon the request of an applicant unless the Secretary finds that the information in the application which would be reviewed by a panel substantially duplicates information which has previously been reviewed by a panel appointed under section [513], "refer such application to the appropriate panel under section [513] for study and for submission (within such period as he may establish) of a report and recommendation respecting approval of the application, together with all underlying data and the reasons or basis for the recommendation.

"(4) If, after receipt of an application under this section, the Secretary determines that any portion of such application is deficient, the Secretary shall provide to the applicant a description of such deficiencies and identify the information required to correct such deficiencies.

"(c) AMENDMENTS TO AN APPLICATION. —

"(1) An applicant may amend an application or supplement to revise or provide additional information.

"(2) An applicant shall amend an application or supplement to provide additional information if such information could reasonably affect an evaluation of whether the relevant standard has been met, or could reasonably affect the statement of contraindications, warnings, precautions, and adverse reactions in the proposed labeling.

"(3) The Secretary may request that an applicant amend an application or supplement with any information necessary for the review of the application or supplement.

"(d) ACTION ON AN APPLICATION FOR PREMARKET APPROVAL. —

"(1) REVIEW. As promptly as possible, but in no event later than [X] days after an application is accepted for submission, unless an extension is necessary to review major amendments under subsection (c), the Secretary, after considering any applicable report and recommendation submitted under paragraph (b)(3), shall –

"(A) Issue an order approving the application if the Secretary finds that all of the grounds for approval in paragraph (2) are met; or

"(B) Deny approval of the application if he finds that one or more grounds for approval in paragraph (2) are not met.

"In making the determination whether to approve or deny the application, the Secretary shall rely on the intended use included in the proposed labeling, if such labeling is not false or misleading based on a fair evaluation of all material facts.

"(2) APPROVAL OR DENIAL OF AN APPLICATION. —

"(A) The Secretary shall approve an application under this section if the Secretary finds that there has been an adequate showing of the following—

"(i) The relevant standard is met;

"(ii) Compliance with applicable quality system requirements set forth in section [QS] or as otherwise specified in a condition of approval;

"(iii) The application does not contain a false statement of material fact;

"(iv) Based on a fair evaluation of all material facts, the proposed labeling is truthful and non-misleading and complies with the requirements in section [labeling];

"(v) The applicant permits authorized FDA employees or persons accredited under this [subchapter/bill name] an opportunity to inspect at a reasonable time and in a reasonable manner the facilities and all pertinent equipment, finished and unfinished materials, containers, and labeling therein, including all things (including records, files, papers, and controls) bearing on whether an in vitro clinical test is adulterated, misbranded, or otherwise in violation of this Act, and permits authorized FDA employees or persons accredited under this Act to view and to copy and verify all records pertinent to the application and the in vitro clinical test;

"(vi) The test conforms in all respects with any applicable performance standards established under section [standards] and complies with any applicable mitigating measures established under section [mitigating measures];

"(vii) All nonclinical laboratory studies that are described in the application and that are essential to show that the test is analytically and clinically valid, were conducted in compliance with the good laboratory practice regulations in 21 CFR part 58, which shall be interpreted to apply to in vitro clinical tests;

"(viii) All clinical investigations involving human subjects described in the application subject to the institutional review board regulations in 21 CFR part 56 and informed consent regulations in 21 CFR part 50, each of which shall be interpreted to apply to in vitro clinical tests, were conducted in compliance with those regulations such that the rights or safety of human subjects were adequately protected; and

"(ix) Such other showings as the Secretary may require.

"(B) An order approving an application may require conditions of approval for the in vitro clinical test, including conformance with performance standards established under section [standards] and compliance with restrictions established under section [restrictions].

"(C) For a first-of-a-kind test, an order approving an application may impose requirements for the test group, including conformance with performance standards established under section [standards], compliance with restrictions established under section [restrictions], and compliance with mitigating measures established under section [mitigating measures]. An approval order for a first-of-a-kind test shall indicate whether subsequent tests in that test group may meet an exemption set forth in section [applicability].

"(D) The Secretary shall publish the approval order on a website of the Food and Drug Administration and make publicly available a summary of the data used to make the decision, except for information restricted from disclosure pursuant to another statute.

"(3) REVIEW FOR DENIALS AND APPROVALS OF APPLICATION. An applicant whose application has been denied approval may, by petition filed on or before the [X] day after the date upon which he receives notice of such denial, obtain review in accordance with section [appeals], and any interested person may obtain review, in accordance with section [appeals], of an order of the Secretary approving an application.

"(e) PROVISIONAL APPROVAL. If the Secretary, after reviewing an application submitted under this section, determines that the applicant has not demonstrated a reasonable assurance of clinical validity, but that the application meets the requirements for provisional approval under section [387C(e)], the Secretary may grant the application provisional approval under section [387C(e)] without regard to whether the application has been designated for priority review under section [387C(c)]. The Secretary shall not grant provisional approval in accordance with this subsection without first notifying the applicant and obtaining authorization from the applicant to so act.

"(f) SUPPLEMENTS TO AN APPLICATION.—

"(1) RISK ANALYSIS. Prior to implementing any modification to an in vitro clinical test, the holder of such approved application shall perform a risk analysis in accordance with section [QS].

"(2) SUPPLEMENT REQUIREMENT.—

"(A) Except as provided in subparagraph (B), or otherwise specified by the Secretary, the holder of an approved application shall submit and receive approval of a supplement before implementing a modification to an approved test.

"(B) The holder of an approved application may implement the following modifications to a test without prior approval of a supplement, provided the holder does not add a manufacturing site, or change activities at an existing manufacturing site, and subject to the requirements of subparagraphs (C) and (D)—

"(i) Modifications included in and implemented in accordance with an approved change protocol;

"(ii) Modifications that

"(I) do not change any of the elements specified in section 587(12) that define a test group;

"(II) do not change performance claims for the in vitro clinical test; or,

"(III) do not change, as applicable, safety of the in vitro clinical test;

"(IV)) do not adversely affect performance of the in vitro clinical test; and

"(V)) do not cause an in vitro clinical test to no longer comply with applicable mitigating measures or restrictions; or

(iii) Labeling changes that are appropriate to address a safety concern.

"(C) A modification described in clause (i) and clause (ii) of subparagraph (B) shall be reported in the next annual report for the test under subsection (h) following the date on which an in vitro clinical test with such modification is introduced into interstate commerce. Such report shall include a description of the modification, and, as applicable, a summary of the analytical and clinical validity, and acceptance criteria.

"(D) A modification referenced in clause (iii) of subparagraph (B) shall be reported to the Secretary within 30 days of the date on which an in vitro clinical test with such modification is introduced into interstate commerce. Any such report shall include—

"(i) A summary of the relevant change or changes;

"(ii) The rationale for implementing such change or changes; and

"(iii) A description of how the change or changes were evaluated.

"Upon review of such report and a finding that the relevant modification is inconsistent with the standard specified under clause (iii) of subparagraph (B), the Secretary may require a supplement under subparagraph (A).

"(3) CONTENTS OF SUPPLEMENT. Unless otherwise specified by the Secretary, a supplement under this subsection shall include–

"(A) For modifications other than manufacturing site changes, a description of the modification, summary or raw data, as applicable, to demonstrate that the relevant standard is met, acceptance criteria, and any revised labeling.

"(B) For manufacturing site changes, the information required in subparagraph (A) and information regarding the methods used in, or the facilities or controls used for, the development of the test to demonstrate compliance with the applicable quality system requirements set forth in section [QS].

"(4) APPROVAL. The Secretary shall approve a supplement if—

"(A) the data, if applicable, demonstrate that the modified test meets the relevant standard; and

"(B) the holder of the approved application has demonstrated compliance with applicable quality system and inspection requirements, where appropriate.

"(5) ADDITIONAL DATA. The Secretary may require, when necessary, additional data to evaluate the modification of the test.

"(6) CONDITIONS OF APPROVAL. An order approving a supplement may require conditions of approval for the in vitro clinical test, including conformance with performance standards established under section [standards] and compliance with restrictions established under section [restrictions].

"(7) PUBLICATION. The Secretary shall publish notice of the supplemental approval order on FDA's website.

"(8) REVIEW OF DENIAL. An applicant whose supplement has been denied approval may, by petition filed on or before the [X] day after the date upon which he receives notice of such denial, obtain review in accordance with section [appeals], and any interested person may obtain review, in accordance with section [appeals], of an order of the Secretary approving a supplement.

"(g) WITHDRAWAL AND TEMPORARY SUSPENSION OF APPROVAL.

"(1) The Secretary may, after providing due notice and an opportunity for informal hearing to the holder of an approved application, issue an order withdrawing approval of the application of an in vitro clinical test if the Secretary finds that –

"(A) The grounds for approval in subsection (d)(2) are no longer met; or

"(B) There is a there is a reasonable likelihood that the in vitro clinical test would cause death or serious adverse health consequences, including by causing the absence, delay, or discontinuation of appropriate medical treatment.

"(2) An order withdrawing approval shall state each ground for withdrawal and shall notify the holder of such withdrawn approval.

"(3) The Secretary shall publish the withdrawal order on the website of the Food and Drug Administration.

"(4) If, after providing an opportunity for an informal hearing, the Secretary determines there is a reasonable likelihood that the in vitro clinical test would cause death or serious adverse health consequences, including by causing the absence, delay, or discontinuation of appropriate medical treatment, the Secretary shall by order temporarily suspend the approval of the application. If the Secretary issues such an order, the Secretary shall proceed expeditiously under paragraph (1) to withdraw such application.

"(h) ANNUAL REPORT.

"(1) Unless the Secretary specifies otherwise, the holder of an approved application shall submit an annual report each year at a time designated by the Secretary in the approval order. Such report shall—

"(A) identify all modifications that an approved application holder has made to any test, including any modification that requires a supplement under subsection (f); and

"(B) include any other information required by the Secretary.

"(2) This annual report requirement shall not apply to in vitro clinical tests that are deemed to have a premarket approval based on a prior clearance under section 510(k) or prior authorization under section 513(f).

"(i) SERVICE OF ORDERS. Orders of the Secretary under this section shall be served (1) in person by any officer or employee of the Department of Health and Human Services designated by the Secretary, or (2) by mailing the order by registered mail or certified mail or electronic equivalent addressed to the applicant at the last known address in the records of the Secretary.

"SEC. 587C. PRIORITY REVIEW

"(a) IN GENERAL.

"(1) An in vitro clinical test that is otherwise required to have approval under section [premarket review] may be designated by the Secretary for priority review in accordance with this section. An application for in vitro clinical test that has been so designated may be granted provisional approval under subsection (e) or approval under subsection (f), in accordance with the requirements of this section.

"(2) An in vitro clinical test for which provisional approval or approval has been granted under this section, and for which such approval is in effect, is exempt from the requirement to obtain premarket approval under section [premarket review].

"(b) ELIGIBILITY.-- An in vitro clinical test is eligible for designation, review, and provisional approval or approval under this section if—

"(1) The test provides or enables more effective treatment or diagnosis of life-threatening or irreversibly debilitating human disease or conditions compared to existing approved or precertified alternatives; and

"(2) It is a test -

"(A) that represents a breakthrough technology;

"(B) for which no approved or precertified alternative exists;

"(C) that offers a clinically meaningful advantage over existing approved or precertified alternatives, including the potential, compared to existing approved or precertified alternatives, to reduce or eliminate the need for hospitalization, improve patient quality of life, facilitate patients' ability to manage their own care (such as through self-directed personal assistance), or establish long-term clinical efficiencies; or

"(D) the availability of which is in the best interest of patients or public health.

"(c) DESIGNATION.

"(1) REQUEST. Except as provided in section [387(e) – provisional approval under premarket review], to receive provisional approval or approval under this section, an applicant must first request that the Secretary designate the in vitro clinical test for priority review. Such a request shall include information demonstrating that the test is eligible for designation under subsection (b).

"(2) DETERMINATION. Not later than 60 calendar days after the receipt of a request under paragraph (1), and prior to acceptance of an application for provisional approval or approval, the Secretary shall determine whether the in vitro clinical test that is the subject

of the request meets the criteria described in subsection (b). If the Secretary determines that the test meets the criteria, the Secretary shall designate the test for priority review.

"(3) REVIEW. Review of a request under paragraph (1) shall be undertaken by a team that is composed of experienced staff and senior managers of the Food and Drug Administration.

"(4) WITHDRAWAL.

"(A) The designation of an in vitro clinical test under this subsection is deemed to be withdrawn, and such in vitro clinical test shall no longer be eligible for review and approval under this section, if—

"(i) the test is deemed not approved under subsection (e)(10);

"(ii) provisional approval for the test is withdrawn under subsection (e)(8); or

"(iii) an application for approval under subsection (f) for the test is denied.

"(B) The Secretary may not withdraw a designation granted under this subsection based on the subsequent approval or precertification of another test that--

"(i) is designated under this section; or

"(ii) was given priority review under section 515C."

"(d) EXPEDITED DEVELOPMENT AND PRIORITY REVIEW.

"(1) For purposes of expediting the development and review of in vitro clinical tests under this section, the Secretary may take the actions and additional actions set forth in section 515B(e) when reviewing such tests under subsection (e) or (f).

"(2) Any reference or authorization in section 515B(e) with respect to a device shall be deemed a reference or authorization with respect to an in vitro clinical test for purposes of this section.

"(e) PROVISIONAL APPROVAL AND APPROVAL.

"(1) APPLICATION FOR PROVISIONAL APPROVAL. Unless otherwise specified by the Secretary, sections [premarket review; (b)(2)(A) – (F), (H)-(K), (b)(3)] apply to applications under this subsection for designated in vitro clinical tests.

"(2) AMENDMENTS. Unless otherwise specified by the Secretary, section [premarket review; (c)] applies to amendments to applications under this subsection.

"(3) ACTION. Unless otherwise specified by the Secretary, sections [premarket review; (d)(1) and (d)(2)(A), (D)] apply to the review, and approval or denial, of applications under this subsection.

"(4) SUPPLEMENTS. Unless otherwise specified by the Secretary, section [premarket review; (ff)] applies to supplements to applications under this subsection.

"(5) CONFIRMATORY POSTMARKET OBLIGATIONS. As set forth in the provisional approval order issued under paragraph (1), the applicant shall—

"(A) Submit within a specified timeframe to the Secretary, and receive approval for, a proposal regarding developing and completing required postmarket studies; and

"(B) Complete the required postmarket studies within the timeframe specified in the provisional approval order, which shall not exceed three years from the date of approval, unless an extension has been granted by the Secretary.

"(6) EXPIRATION. Provisional approval under paragraph (1) shall expire on—

"(A) the date that is specified in the provisional approval order, except that if an application for approval is submitted three months before this date in accordance with subparagraph (8)(B), on the date that the Secretary makes a decision on such application;

"(B) the date that is specified in an order issued by the Secretary that amends the provisional approval timeframe, except that if an application for approval is submitted three months before this date in accordance with subparagraph (8)(B), on the date the Secretary makes a decision on such application; "(C) the date on which provisional approval is withdrawn under paragraph (11) of this subsection.

"(7) LABELING. Any in vitro clinical test that is provisionally approved shall include in labeling a statement that the test is "provisionally approved with confirmatory postmarket obligations."

"(8) APPLICATION FOR APPROVAL.

"(A) Any holder of a provisional approval may submit an application for approval, which shall contain the information required under section [587B(b)]. Such application may incorporate by reference information from the application for provisional approval for that in vitro clinical test.

"(B) An application for approval under this paragraph shall be submitted at least three months before the date that provisional approval expires under subparagraph (A) or (B) of paragraph (6).

"(C) Applications for approval shall be reviewed in accordance with the procedures and requirements of section [premarket review – 387B(b)–(d), (f)], subject to any actions or additional actions taken by the Secretary under subsection (d). In reviewing such an application, the relevant standard shall be a reasonable assurance of analytical and clinical validity.

"(9) REVIEW FOR DENIALS AND APPROVALS OF APPLICATION. An applicant whose application has been denied provisional approval or approval under this subsection may, by petition filed on or before the [X] day after the date upon which he receives notice of such denial, obtain review in accordance with section [appeals], and any interested person may obtain review, in accordance with section [appeals], of an order of the Secretary approving an application.

"(10) TEST DEEMED NOT APPROVED. A test for which provisional approval has been granted under this subsection shall be deemed not approved on–

"(A) The date that provisional approval expires under paragraph (6), unless an application for approval under paragraph (8) has been approved prior to such date;

"(B) The date on which a denial of approval order is issued under paragraph (8)(C), if the applicant does not appeal the order under subsection (f)(4) and if such denial occurs prior to the date of expiration of provisional approval; or

"(C) The date on which the Director of the Center for Devices and Radiological Health or the Director of the Center for Biologics Evaluation and Research, whichever is appropriate, issues a decision on an appeal regarding an application for approval, if such decision occurs prior to the date of expiration of provisional approval.

"(11) WITHDRAWAL.

"(A) The Secretary may, based on new valid scientific evidence and after providing due notice and an opportunity for an informal hearing, issue an order withdrawing the provisional approval of an in vitro clinical test under this subsection if the Secretary determines that—

"(i) the test no longer meets the relevant standard; or

"(ii) the test presents an unreasonable risk to human health.

"(B) An order withdrawing approval shall state each ground for withdrawal and shall notify holders of such applications that they may, by petition filed on or before the [thirtieth] day after the date upon which he receives notice of such withdrawal, obtain review under section [appeals].

"(C) The Secretary shall provide notice of the withdrawal order on the website of the Food and Drug Administration.

"(f) ANNUAL REPORT. Unless otherwise specified by the Secretary, section [premarket approval; (g)] requiring annual reports applies to in vitro clinical tests provisionally approved or approved under this subsection.

"(g) SERVICE OF ORDERS. Orders of the Secretary under this section shall be served (1) in person by any officer or employee of the Department of Health and Human Services designated by the Secretary, or (2) by mailing the order by registered mail or certified mail or electronic equivalent addressed to the applicant at his last known address in the records of the Secretary.

"(h) STATUTORY CONSTRUCTION—The term "approval" when used throughout this title generally does not include provisional approval and does include approval under paragraph (8) of subsection (e).

"SEC. 587D. PRECERTIFICATION.

"(a) IN GENERAL. —

"(1) Any eligible person may seek precertification in accordance with this section.

"(2) An in vitro clinical test is exempt from premarket review under section 587A if its developer is precertified under this section and the in vitro clinical test—

"(A) is an eligible in vitro clinical test under subsection (b)(2); and

"(B) falls within the scope of a precertification order issued under this section, and such order is in effect.

"(b) ELIGIBILITY. —

"(1) ELIGIBLE PERSON. — As used in this section, the term 'eligible person' means an in vitro clinical test developer unless, at the time such person seeks or would seek precertification, the person—

"(A) has been found to have committed a significant violation of this Act or the Public Health Service Act, except that this subparagraph shall not apply if—

"(i) such violation occurred more than five years prior to the date on which such precertification is or would be sought;

"(ii) such violation has been resolved; or

"(iii) such violation is not pertinent to any in vitro clinical test within the scope of the precertification that such person seeks or would seek; or

"(B) has been disqualified by the Secretary on the basis of actions or omissions that raise serious questions regarding whether the eligibility of such person would be in the interest of public health, such as—

"(i) making false or misleading statements about matters relevant under this subchapter;

"(ii) failing to maintain required certifications under section 353 of the Public Health Service Act (42 U.S.C. 263a); or

"(iii) violating any requirement of this Act or the Public Health Service Act, where such violation exposes persons to serious risk of illness, injury, or death.

"(2) ELIGIBLE IN VITRO CLINICAL TEST.—An in vitro clinical test is eligible under subsection (a)(2) for exemption from premarket review under section 587A except as provided in this paragraph.

"(A) An in vitro clinical test is not eligible for an exemption from premarket review if it is—

"(i) a component, part, or accessory of an in vitro clinical test as described under section 201(ss)(1)(E);

"(ii) a test platform under section 201(ss)(1)(B);

"(iii) an article for taking or deriving specimens from the human body under section 201(ss)(1)(C);

"(iv) software under section 201(ss)(1)(D), unless such software itself identifies, diagnoses, screens, measures, detects, predicts, prognoses, analyzes, or monitors a disease or condition, including a determination of the state of health, or itself selects, monitors, or informs therapy or treatment for a disease or condition;

"(v) a first-of-a-kind in vitro clinical test;

"(vi) a test system for home use;

high risk in vitro clinical test; or

"(vii) an in vitro clinical test, including reagents used in such tests, intended for use—

"(I) in the collection, manufacture, or use of blood and blood components intended for transfusion or further manufacturing use or the recovery, manufacture, or use of human cells, tissues, and cellular and tissue-based products intended for implantation, transplantation, infusion, or transfer into a human recipient, including tests intended for use in determination of donor eligibility, donation suitability, and compatibility between donor and recipient;

"(II) in the diagnosis, monitoring, or treatment of hemolytic disease of the newborn, including tests intended for use in determination of compatibility between mother and newborn; or

"(III) in the diagnosis or monitoring of human retroviruses or human retrovirus infection.

"(B) For a cross-referenced in vitro clinical test or a direct-to-consumer in vitro clinical test, such test shall be eligible for precertification only upon a determination by the Secretary that eligibility is appropriate on the basis of the mitigating measures applicable to such test. Notwithstanding subchapter II of chapter 5 of title 5, any determination by the Secretary under this subparagraph—

"(i) shall take effect if it is published in the Federal Register with an accompanying rationale; and

"(ii) may be revoked if the Secretary publishes a proposed revocation in the Federal Register, provides an opportunity for comment, and publishes a final revocation after consideration of the comments.

"(c) APPLICATION FOR PRECERTIFICATION. —

"(1) IN GENERAL -- A person seeking precertification [ ][] shall submit an application under this subsection, which shall contain the information specified under paragraph (2).

"(2) CONTENTS OF APPLICATION -- An application for precertification shall contain—

"(A) A statement identifying the scope of the proposed precertification, which shall be no broader than a single technology (i.e., test method) and a single medical subspecialty (such as would be described by the combination of a test purpose and disease or condition), consistent with the procedures for analytical validation and clinical validation included in the application;

"(B) Information showing that the person seeking precertification is an eligible person under subsection (b)(1);

"(C) Information showing that the methods used in, and the facilities and controls used for, the development of all eligible in vitro clinical tests within the proposed scope of precertification conform to the quality system requirements of section [quality systems];

"(D) Procedures for analytical validation, including all procedures for validation, verification, and acceptance criteria, and an explanation as to how such procedures, when used, provide a reasonable assurance of analytical validity of all eligible in vitro clinical tests within the proposed scope of precertification;

"(E) Procedures for clinical validation, including all procedures for validation, verification, and acceptance criteria, and an explanation as to how such procedures, when used, provide a reasonable assurance of clinical validity of all eligible in vitro clinical tests within the proposed scope of precertification;

"(F) A notification under section [x] for each in vitro clinical test that would be precertified under the application for precertification and would be introduced or delivered for introduction into interstate commerce upon the issuance of the precertification order;

"(G) Information concerning one or more representative in vitro clinical tests, including—

"(i) The information specified in [premarket submission content requirements] for the representative in vitro clinical test or tests, except that raw data shall be provided for any such in vitro clinical test unless the Secretary determines otherwise;

"(ii) An explanation of how the representative in vitro clinical test or tests adequately represent the range of procedures included in the application under subparagraphs (C), (D), (E), and (F);

"(iii) A narrative description of how the procedures included in the application under subparagraphs (C), (D), (E), and (F) have been applied to the representative in vitro clinical test or tests; and

"(H) Such other information relevant to the subject matter of the application as the Secretary may require.

"(d) ACTION ON AN APPLICATION FOR PRECERTIFICATION. —

"(1) As promptly as possible, but in no event later than __ days after receipt of an application under subsection (c), the Secretary shall—

"(A) Issue a precertification order granting the application, which shall specify the scope of the precertification, if the Secretary finds that all of the grounds in paragraph (3) are met; or

"(B) Deny the application if the Secretary finds (and sets forth the basis of such finding as part of or accompanying such denial) that one or more grounds for granting the application specified in paragraph (3) are not met.

"(2) If, after receipt of an application under this section, the Secretary determines that any portion of such application is deficient, the Secretary shall provide to the applicant a

description of such deficiencies and identify the information required to correct such deficiencies.

"(3) The Secretary shall grant an application under this section if, on the basis of the information submitted to the Secretary as part of the application and any other information before him or her with respect to such applicant, the Secretary finds that—

"(A) There is a showing of reasonable assurance of analytical validity for all eligible in vitro clinical tests within the proposed scope of the precertification, as evidenced by the procedures for analytical validation;

"(B) There is a showing of reasonable assurance of clinical validity for all eligible in vitro clinical tests within the proposed scope of the precertification, as evidenced by the procedures for clinical validation;

"(C) The methods used in, or the facilities or controls used for, the development of all eligible in vitro clinical tests within the proposed scope of the precertification conform to the requirements of section [quality systems];

"(D) Based on a fair evaluation of all material facts, the applicant's labeling and advertising is not false or misleading in any particular;

"(E) The application does not contain a false statement of material fact;

"(F) There is a showing that the representative in vitro clinical test or tests—

"(i) meets the standard for approval under section [premarket review standard]; and

"(ii) adequately represent the range of procedures for analytical validation and clinical validation included in the application; and

"(G) The applicant permits authorized employees of the Food and Drug Administration or persons accredited under this Act an opportunity to inspect at a reasonable time and in a reasonable manner the facilities and all pertinent equipment, finished and unfinished materials, containers, and labeling therein, including all things (including records, files, papers, and controls) bearing on whether an in vitro clinical test is adulterated, misbranded, or otherwise in violation of this Act, and permits such authorized employees or persons accredited under this Act to view and to copy and verify all records pertinent to the application and the in vitro clinical test;

"(4) An applicant whose application has been denied may, by petition filed on or before the date that is 30 calendar days after the date upon which such applicant receives notice of such denial, obtain review thereof in accordance with section [appeals].

"(e) DURATION; SUBSEQUENT SUBMISSIONS. —

"(1) A precertification order under subsection (d)(1)(A) shall remain in effect until the earliest of—

"(A) the expiration of such precertification order under paragraph (2); or

"(B) the withdrawal of such precertification order under subsection (h).

"(2) A precertification order under subsection (d)(1)(A) shall expire on the date that is two years after the date that such order is issued, except that if an application for renewal under paragraph (3) has been received not later than __ days prior to the expiration of such order under this paragraph, such order shall expire on the date on which the Secretary has granted or denied the application for renewal.

"(3)(A) Any person with a precertification order in effect with respect to development of in vitro clinical tests may seek renewal of such order provided that –

"(i) such person is an eligible person under subsection (b)(1); and

"(ii) none of the information specified in subsection (c)(2) has changed.

"(B) An application for renewal under this paragraph shall include information concerning one or more representative in vitro clinical tests in accordance with subsection (c)(2)(G), except that such representative test or tests shall be different from the representative test or tests included in any prior application.

"(C) The Secretary's action on an application for renewal of precertification under this paragraph shall be conducted in accordance with subsection (d), and any order resulting from such application shall be treated as a precertification order for purposes of this subchapter.

"(4) SUPPLEMENTS; REPORTS. —

"(A) Except as provided in subparagraph (B), any person with a precertification order in effect may seek a supplement to such order upon a change or changes to the information provided in the application for precertification under subparagraphs (C), (D), and (E) of subsection (c)(2), provided that such person is an eligible person under subsection (b)(1) and that such change does not expand the scope of the precertification. A supplement may contain only information relevant to the change or changes. The Secretary's action on a supplement shall be in accordance with subsection (d), and any order resulting from such supplement shall be treated as an amendment to a precertification order that is in effect.

"(B) If a change or changes described in subparagraph (A) is made in order to address a potential risk to public health by adding a new specification or test method, the person may immediately implement such change or changes and shall report such changes or changes to the Secretary within 30 days.

"(i) Any report to the Secretary under this subparagraph shall include—

"(I) A summary of the relevant change or changes;

"(II) The rationale for implementing such change or changes; and

"(III) A description of how the change or changes were evaluated.

"(ii) Upon review of such report and a finding that the relevant change or changes are inconsistent with the standard specified under this subparagraph, the Secretary may require a supplement under subparagraph (A).

"(f) MAINTENANCE REQUIREMENTS. — For the duration of a precertification under subsection (e)(1), a holder of a precertification order shall—

"(1) use the procedures included in the relevant application, supplement, or report under subsections (b) and (e);

"(2) ensure compliance with any applicable mitigating measures;

"(3) maintain, and provide to the Secretary upon request, records related to any precertified in vitro clinical test that are pertinent to matters under this Act; and

"(4) Comply with the notification requirements under section [notification] for each precertified in vitro clinical test.

"(g) TEMPORARY HOLD. —

"(1) Upon one or more findings under paragraph (3), the Secretary may prohibit any holder of a precertification order from introducing into interstate commerce an in vitro clinical test that was not previously the subject of a notification under section [notification] (referred to in this subsection as a "temporary hold").

"(2) Such temporary hold shall be removed upon resolution of the relevant finding or findings under paragraph (3).

"(3) GROUNDS FOR TEMPORARY HOLD. — A temporary hold under this subsection may be instated upon a finding or findings that the holder of a precertification order—

"(A)is not in compliance with any maintenance requirements under subsection (f);

"(B)labels or advertises one or more in vitro clinical tests with false or misleading claims; or

"(C)is no longer an eligible person under subsection (b)(1).

"(h) WITHDRAWAL. — The Secretary may, after due notice and opportunity for informal hearing, issue an order withdrawing a precertification order if the Secretary finds that

"(1) the application, supplement, or report under subsections (b) or (e) contains false or misleading information or fails to reveal a material fact; or

"(2) such holder fails to correct false or misleading labeling or advertising upon the request of the Secretary;

"(3) in connection with a precertification, the holder provides false or misleading information to the Secretary; or

"(4) the holder of such precertification order fails to correct the grounds for temporary hold within a timeframe specified in the precertification order.

"SEC. 587E. MITIGATING MEASURES

"(a) DEFINITION. The term 'mitigating measures' shall have the meaning set forth in section [Definitions587(10)].

"(b) ESTABLISHMENT OF MITIGATING MEASURES--

"(1) ESTABLISHING, CHANGING, OR WITHDRAWING –

"(A) If the Secretary determines that the establishment of mitigating measures is necessary for any of the reasons identified in [definitions section] for any test group or test groups, the Secretary may require that tests in such group or groups comply with such mitigating measures.

"(B) The Secretary may establish, change, or withdraw mitigating measures by administrative order published in the Federal Register following publication of a proposed mitigating measure order and consideration of comments to a public docket, notwithstanding subchapter II of chapter 5 of title 5, United States Code.

"(2) In Vitro Clinical Tests Previously Regulated As Devices –

"(A) Any special controls or restrictions applicable to an in vitro clinical test or test group based on prior regulation as a device, including those established in the period from the enactment date to the effective date of this [subchapter/bill name], shall continue to apply to such test or test group after this[subchapter/bill name] takes effect. Such special controls or restrictions shall be deemed mitigating measures upon the effective date of this [subchapter/bill name].

"(B) The Secretary may establish, change, or withdraw mitigating measures for such test or test group using the procedures under paragraph (1).

"(c) DOCUMENTATION—

"(1) The developer of an in vitro clinical test subject to premarket review and to which mitigating measures apply must, in accordance with [section 587C(b)(2)(D) of premarket review] submit documentation to the Secretary as part of its premarket application demonstrating that such mitigating measures have been met. If such application is approved, such developer shall maintain documentation demonstrating that such mitigating measures continue to be met, and must make such documentation available to the Secretary upon request or inspection.

"(2) The developer of an in vitro clinical test that is marketed within the scope of a precertification or other exemption from premarket review and to which mitigating measures apply must –

"(A) maintain documentation in accordance with the quality systems requirements in [section QS] demonstrating that such mitigating measures have been met, and must make such documentation available to the Secretary upon request or inspection; and

"(B) include in the performance summary for such test a description of how such mitigating measures are met, if applicable.

[*Add adulteration/misbranding/prohibited act for failure to comply with mitigating measures*]

"SEC. 587F. RISK REDESIGNATION.

"(a) Based on new information, including the establishment of mitigating measures under [], and after considering all available evidence respecting a test group, the Secretary may, upon the initiative of the Secretary or upon petition of an interested person ---

"(1) change the risk designation of such test group;

"(2) revoke any exemption or requirement in effect with respect to such test group; or

"(3) determine that a test group or test groups subject to premarket review is eligible for precertification, consistent with section 587D(b)(2)(B), or other exemptions.

"(b) Any action under subsection (a) shall be made by publication of a notice of such proposed action in the Federal Register, consideration of comments to a public docket on such proposal, and publication of a final notice in the Federal Register, notwithstanding subchapter II of chapter 5 of title 5, United States Code.

"SEC. 587G. ADVISORY COMMITTEES [placeholder]

"SEC. 587H. REQUEST FOR INFORMAL FEEDBACK

PRESUBMISSION MEETINGS.—The Secretary shall establish a program for stakeholders to request meetings to discuss which regulatory pathway is appropriate for an in vitro clinical test, a future premarket application for an in vitro clinical test, or a precertification package for an in vitro clinical test.

"SEC. 587I. REGISTRATION AND NOTIFICATION.

"(a) REGISTRATION OF ESTABLISHMENTS FOR IN VITRO CLINICAL TESTS.

"(1) Each person who is an in vitro clinical test developer— or a contract manufacturer (including contract packaging), contract sterilizer, repackager, relabeler, distributor, or a person who introduces or proposes to begin the introduction or delivery for introduction into interstate commerce any in vitro clinical test—— shall –

"(A) During the period beginning on October 1 and ending on December 31 of each year, register with the Secretary the name of such person, places of business of such person, all establishments engaged in the activities specified under this paragraph, the unique facility identifier of each such establishment, and a point of contact for each such establishment, including an electronic point of contact; and

"(B) Submit an initial registration containing the information required under subparagraph (A) not later than—

"(i) the date of implementation of this section if such establishment is engaged in any activity described in this paragraph on the date of enactment of this section, unless the Secretary establishes by guidance a date later than such implementation date for all or a category of such establishments; or

” (ii) thirty days prior to engaging in any activity described in this paragraph after enactment of this section, if such establishment is not engaged in any activity described in this paragraph on the date of enactment of this section.

“(2) The Secretary may assign a registration number or unique facility identifier to any person or any establishment registered in accordance with this section. Registration information shall be made publicly available by publication on the website maintained by the Food and Drug Administration.

“(3) Every person or establishment that is required to be registered with the Secretary under this section shall be subject to inspection pursuant to section 704.

“(b) NOTIFICATION INFORMATION FOR IN VITRO CLINICAL TESTS.

“(1) Each developer of an in vitro clinical test shall submit a notification to the Secretary containing the information described in this subsection in accordance with the applicable schedule described under subsection (c). Such notification shall be prepared in such form and manner as the Secretary may specify in guidance. Notification information shall be submitted to the comprehensive test information system in accordance with section XX.

“(2) Each developer shall electronically submit to the comprehensive test information system the following information for each in vitro clinical test for which such person is a developer in the form and manner prescribed by the Secretary:

“(A) name of the establishment and its unique facility identifier;

“(B) contact information for the official correspondent for the notification;

“(C) name (common name and trade name, if applicable) of the in vitro clinical test; and its test notification number (when available).

“(D) CLIA certificate number for any laboratory certified by the Secretary under section 263a of title 42 that meets the requirements for performing high-complexity testing that is the developer of the in vitro clinical test, and CLIA certificate number for any laboratory under common ownership that is performing the test developed by such test developer;

“(E) the appropriate category under this subchapter under which the in vitro clinical test is offered, introduced or marketed, such as — precertification, low-risk exemption, premarket approval, grandfathering, or another specified category;

“(F) brief narrative description of the in vitro clinical test;

“(G) substance or substances measured by the in vitro clinical test, such as analyte, protein, or pathogen;

“(H) type or types of specimen or sample;

“(I) test method;

“(J) test purpose, as described in section 201(ss)(1)(A), such as screening, predicting, or monitoring;

“(K) disease or condition for which the in vitro clinical test is intended for use;

"(L) intended patient population;

"(M) context of use, such as in a clinical laboratory, in a health care facility, prescription home use, over-the-counter use, or direct-to-consumer testing.

"(N) summary of in vitro clinical test analytical performance and clinical performance, and as applicable lot release criteria;

"(O) statement describing conformance with applicable mitigating measures, restrictions, and standards;

"(P) representative labeling for the in vitro clinical test; and

"(Q) a certification that the information submitted is truthful and accurate.

"(3) The Secretary may assign a test notification number to each in vitro clinical test that is the subject of a notification under this section. The process for assigning test notification numbers may be established through guidance, and may include the recognition of standards, formats, or conventions developed by a third-party organization.

"(4) A person who is not a developer but is otherwise required to register pursuant to subsection (a) shall submit an abbreviated notification to the Secretary containing the information described in subparagraphs (A) through (C) of paragraph (2), the name of the developer, and any other information described in paragraph (2) as may be specified by the Secretary in guidance, as applicable to the activities of each class of persons required to register. The information shall be submitted in accordance with the applicable schedule described under subsection (c). Such abbreviated notification shall be prepared in such form and manner as the Secretary may specify in guidance. Notification information shall be submitted to the comprehensive test information system in accordance with section XX.

"(c) TIMELINES FOR SUBMISSION

"(1) For an in vitro clinical test that was listed as a device under section 510(j) prior to the date of enactment of this section, a person shall maintain a device listing under section 510 until such time as the system for submitting the notification information required under subsection (b) becomes available to in vitro clinical test developers, and thereafter shall submit the notification information no later than [X].

"(2) For an in vitro clinical test that is subject to the grandfathering provisions of section 587Xxx, a person shall submit the notification information required under subsection (b) no later than X months after the system for submitting the notification becomes available.

"(3) For an in vitro clinical test that is not subject to paragraph (1) or (2), a person shall submit the required notification information prior to offering, introducing, or marketing the in vitro clinical test as follows:

"(A)for an in vitro clinical test that is not exempt from premarket approval, a person shall submit the required notification information no later than ten business days after the date of approval of the premarket approval application;

"(B)for an in vitro clinical test that is exempt from premarket approval, a person shall submit the required notification information at least ten business days prior

to offering the in vitro test for clinical use or otherwise introducing the in vitro clinical test into interstate commerce.

“(4) Each person required to submit notification information under this section shall update such information within ten business days of any change that causes any previously notified information to be inaccurate or incomplete.

"(5) Each person required to submit notification information under this section shall update its information annually during the period beginning on October 1 and ending on December 31 of each year and certify that the information contained in such notification is truthful and accurate, and shall pay the annual notification fee prescribed in section XXX.

“(d) PUBLIC AVAILABILITY OF NOTIFICATION INFORMATION.

“(1) Notification information submitted pursuant to this section shall be made publicly available by publication on the website of the Food and Drug Administration after the in vitro clinical test developer has certified the information as truthful and accurate.

“(2) Notification information for an in vitro clinical test that is subject to premarket approval or precertification shall remain confidential until such date as the in vitro clinical test receives the applicable premarket approval or precertification.

“(3) The registration and notification information requirements described in subsections (a) and (b) shall not apply to the extent the Secretary determines that such information is restricted from disclosure pursuant to another statute, including information relating to national security or countermeasures.

“SEC. 587J.

QUALITY SYSTEM REQUIREMENTS

“(a) APPLICABILITY.

“(1) Each developer and each other person required to register undersection 587I(a)(1) shall establish and maintain a quality system in accordance with the applicable requirements set forth in subsection (b), except as provided in section [applicability].

“(2) A developer that operates its own clinical laboratory certified by the Secretary under section 263a of title 42 of the United States Code that meets the requirements for performing high-complexity testing and develops its own in vitro clinical test or tests or modifies another developer’s in vitro clinical test in that certified laboratory in a manner described in [developer definition], where such in vitro clinical test or in vitro clinical tests are for use only within that certified laboratory, shall establish and maintain with respect to such test or tests a quality system that complies with the requirements set forth in subsection (b)(2). The applicable requirements set forth in subsection (b)(1) shall apply to any test platform, article for taking or deriving specimens from the human body, component, part or accessory that is developed for use by a clinical laboratory to which the first sentence of this paragraph applies.

“(3) A clinical laboratory certified by the Secretary under section 263a of title 42 of the United States Code that meets the requirements for performing high-complexity testing

must comply with the applicable quality system requirements under subsection (b) no later than the date of implementation of this subchapter.

"(4) As necessary, the Secretary shall amend part 820 of title 21 of the Code of Federal Regulations, or successor regulations, to implement the provisions of this [section]. In considering such amendment, the Secretary shall consider whether and to what extent international harmonization might be appropriate. Until such amendment takes effect, such regulations shall be interpreted to apply to in vitro clinical tests and developers.

"(5) The Secretary may establish such other regulations under this section as are necessary to assure the analytical and clinical validity of in vitro clinical tests, or the safety of articles for taking or deriving specimens from the human body.

"(b) QUALITY SYSTEM REQUIREMENTS.

"(1) IN GENERAL—-- For—-- For purposes of establishing quality system requirements under this [section], including applying or amending 21 CFR part 820 as provided in subsection (a)(4), the quality system requirements applicable to in vitro clinical tests shall include each of the following, subject to paragraphs (2) and (3):

"(A) management responsibility;

"(B) quality audit;

"(C) personnel;

"(D) design controls;

"(E) document controls;

"(F)purchasing controls, including supplier controls;

"(G) identification and Traceability;

"(H) production and process controls;

"(I) acceptance activities;

"(J) nonconforming product;

"(K) corrective and preventive action;

"(L) labeling and packaging controls;

"(M) handling, storage, distribution, and installation;

"(N) records;

"(O) servicing; and

"(P) statistical techniques.

"(2) QUALITY SYSTEM REQUIREMENTS FOR CERTAIN LABORATORIES.— With regard to establishing quality system requirements under this Act, including applying or amending 21 CFR part 820 as provided in subsection (a)(4), quality system requirements applicable to the in vitro clinical tests and developers described in subsection (a)(2) shall consist of the following:

"(A) design controls;

"(B) purchasing controls, including supplier controls;

(C) acceptance activities;

"(D) corrective and preventative action; and

"(E) records.

"(3) QUALITY SYSTEM REQUIREMENTS FOR CERTAIN LABORATORIES DISTRIBUTING PROTOCOLS.—

"(A) With regard to establishing quality system requirements under this Act, including applying or amending 21 CFR part 820 as provided in subsection (a)(4), quality system requirements applicable to the developer and in vitro clinical test distributed under subparagraph (B) shall consist of the following provided that the conditions of subparagraph (B) are met —

"(i) the requirements in paragraph (2),

"(ii) the labeling requirements in subparagraph (1)(L), and

"(iii) the requirement to maintain records of the laboratories to which the test protocol is distributed.

"(B) To be eligible for subparagraph (A), the following conditions must be met—

"(i) the laboratory distributing the protocol is certified by the Secretary under section 263a of title 42 of the United States Code and meets the requirements for performing high-complexity testing;

"(ii) the laboratory develops its own in vitro clinical test or modifies another developer's in vitro clinical test in a manner described in [Section 587(6)]; and

"(iii) the laboratory distributes the test protocol for such test only to another laboratory that—

(I) is certified by the Secretary under section 263a of title 42 of the United States Code and meets the requirements for performing high-complexity testing; and

"(II) is within the same corporate organization and having common ownership by the same parent corporation; or as applicable, is within the Laboratory Response Network of the Centers for Disease Control and Prevention.

"SEC. 587K. LABELING REQUIREMENTS.

"(a) IN GENERAL. An in vitro clinical test shall bear or be accompanied by labeling, and a label as applicable, that meet the requirements set forth in subsections (b) and (c), and any other requirements established by the Secretary by regulations, unless such test is exempt as specified in subsection (d) or (e).

"(b) LABELS. —

"(1) The label of an in vitro clinical test shall meet the requirements set forth in paragraph (2), except this requirement shall not apply to an in vitro clinical test that consists solely of a test protocol, or that is designed, manufactured, and used solely within a single laboratory certified by the Secretary under section 263a of title 42 that meets the requirements for performing high-complexity testing.

"(2) The label of an in vitro clinical test shall state the name and place of business of its developer and meet the requirements set forth in section 809.10(a) of title 21 of the Code of Federal Regulations, or any successor regulation. The Secretary shall amend such regulation, as necessary, to ensure its applicability to in vitro clinical tests. Until such amendment takes effect, such regulations shall be interpreted to apply to in vitro clinical tests.

"(c) LABELING. —

"(1) Labeling accompanying an in vitro clinical test, including labeling in the form of a package insert, standalone laboratory reference document, or other similar document except the labeling specified in paragraph (2), shall include adequate directions for use and shall meet the requirements set forth in section 809.10(b) and (g) of title 21 of the Code of Federal Regulations, or any successor regulation, except as provided in subsection (d). Labeling in the form of a package insert shall also include the information in subparagraphs (2)(A) through (C). The Secretary shall amend such regulation, as necessary, to ensure its applicability to in vitro clinical tests. Until such amendment takes effect, such regulation shall be interpreted to apply to in vitro clinical tests.

"(2) Labeling accompanying an in vitro clinical test that is in the form of a test report template or ordering information shall include

"(A) The test notification number that was provided to the developer at the time of notification;

"(B) Instructions for how and where to report an adverse event under section [Adverse Events], such as "Please report adverse events related to this test to the FDA at X."; and

"(C) Instructions for how and where to access the performance summary data displayed in the notification database for the test.

(D)The intended use of the in vitro clinical test;

(E) Any warnings,

(F) Contraindications, and

(G) Limitations.

"(3) Labeling for an in vitro clinical test [used for] immunohematology testing shall meet the following additional requirements set forth in part 660 of the Code of Federal Regulations (or any successor regulation), as they appear on the date of enactment of this subchapter if to the extent such test fell within the scope of such regulations immediately prior to such date of enactment:

(A) Section 660.28 (a)(1)(i); (a)(1)(ii)(A) and (F); (a)(2)(i) and (xiv); and (a)(4);

(B) Section 660.35 (a)(1)(ii); (a)(2) - (4); (a)(6) - (9); and

(C) Section 660.55 (a)(1)(i); (a)(1)(ii)(A) and (H).

The Secretary shall amend such regulations, as necessary, to ensure their applicability to in vitro clinical tests. Until such amendment takes effect, such regulations shall be interpreted to apply to in vitro clinical tests.

"(d) EXEMPTIONS AND ALTERNATIVE REQUIREMENTS.

"(1) For an in vitro clinical test that is designed, manufactured, and used solely within a single high complexity laboratory certified by the Secretary under section 353353 of the Public Health Service Act, and owned and operated by the developer of such in vitro clinical test, the requirement in section 809.10(b) of title 21 of the Code of Federal Regulations that the labeling "state in one place" all of the required information may be satisfied by the laboratory posting such required information on its website or in multiple documents, if such documents are maintained and accessible in one place.

"(2) The labeling for a test platform, when such platform is not committed to specific diagnostic procedures or systems, is not required to bear the information indicated in paragraphs (3), (4), (5), (7), (8), (9), (10), (11), (12), and (13) of section 809.10(b) of title 21 of the Code of Federal Regulations, as it appears on the date of enactment of this subchapter and amended thereafter.

"(3) For purposes of compliance with subsection (c)(1), the labeling for a reagent intended for use as a replacement in a diagnostic system may be limited to that information necessary to identify the reagent adequately and to describe its proper use in the system.

"(4) LAB RESEARCH OR INVESTIGATIONAL USE. A shipment or other delivery of an in vitro diagnostic test shall be exempt from the requirements of subsection (b) and (c)(1) and from any standard promulgated under part 861 of title 21 of the Code of Federal Regulations, or any successor regulation, provided that the conditions set forth in 809.10(c) of such title, as it appears on the date of enactment of this subchapter and amended thereafter are met. The Secretary shall amend such regulations, as necessary, to ensure their applicability to in vitro clinical tests. Until such amendment takes effect, such regulations shall be interpreted to apply to in vitro clinical tests.

"(5) GENERAL PURPOSE LABORATORY REAGENTS. The labeling of general purpose laboratory reagents, such as hydrochloric acid, whose uses are generally known by persons trained in their use need not bear the directions for use required by subsection (b) and subsection (c)(1).

"(6) ANALYTE SPECIFIC REAGENTS. The labeling of analyte specific reagents, such as monoclonal antibodies, deoxyribonucleic acid (DNA) probes, viral antigens, ligands and other similar items, shall bear the information set forth in 21 C.F.R. 809.10(e)(1) through (2) as it appears on the date of enactment of this subchapter and amended thereafter and shall bear the following statement - "This product is intended solely for further

development of an in vitro clinical test and is exempt from most FDA regulation. This product must be evaluated by the in vitro clinical test developer in accordance with supplier controls if it is used with or in the development of an in vitro clinical test.". If the labeling of an analyte specific reagent bears the information set forth in this paragraph, it need not bear the information required by subsection (c)(1).

"(7) The labeling for over-the-counter (OTC) test sample collection systems for drugs of abuse testing shall bear the name and place of business of the developer and the information specified in 21 C.F.R. 809.10(f) as it appears on the date of enactment of this subchapter and amended thereafter, in language appropriate for the intended users. If the labeling of such OTC test sample collection system bears the information set forth in this paragraph (4)(G), it need not bear the information required by subsection (c)(1).

"(8) The labeling for an in vitro clinical test approved under [subsection (d) of priority review/provisional approval section], until approved under [subsection (e) of that section], or approved under [subsection (e) of premarket review], until approved under that section, shall bear a statement that the test is "provisionally approved with confirmatory postmarket obligations."

"(e) TESTS IN THE STRATEGIC NATIONAL STOCKPILE.

"(1) The Secretary may grant an exception or alternative to any provision listed in this section, unless explicitly required by a statutory provision outside this section, for specified lots, batches, or other units of an in vitro clinical test, if the Secretary determines that compliance with such labeling requirement could adversely affect the safety, effectiveness, or availability of such products that are or will be included in the Strategic National Stockpile.

"(2) The Secretary may issue regulations amending section 809.11 of title 21 of the Code of Federal Regulations or any successor regulation to apply in full or in part to in vitro clinical tests and in vitro clinical test developers.

"(f) The Secretary may, in collaboration with developers, issue guidance on standardized, general content and format for in vitro clinical test labeling to help ensure compliance with applicable requirements in this subsection."

"SEC. 587L. ADVERSE EVENT REPORTING.

"(a) APPLICABILITY.

"(1) Each in vitro clinical test developer shall establish, maintain, and implement a system for reporting adverse events in accordance with subsection (b), except as provided in section [applicability].

"(2) The Secretary shall amend part 803 of Title 21 of the Code of Federal Regulations (or any successor regulations) to apply to in vitro clinical tests. Until such amendment takes effect, such part shall be interpreted to apply to in vitro clinical tests.

"(3) The Secretary may by regulation require reporting of such other adverse event experiences as determined by the Secretary to be necessary to be reported to assure the analytical and clinical validity of in vitro clinical tests, and in addition, the safety of articles for taking or deriving specimens from the human body.

"(b) ADVERSE EVENT REPORTING REQUIREMENTS.

"(1) Each in vitro clinical test developer shall report to the Secretary whenever the developer receives or otherwise becomes aware of information that reasonably suggests that one of its in vitro clinical tests–

"(A) may have caused or contributed to a death or serious injury, or

"(B) has malfunctioned and the in vitro clinical test, or a similar in vitro clinical test developed or marketed by the in vitro clinical test developer, would be likely to cause or contribute to a death or serious injury if the malfunction were to recur, and

"(C) such adverse event cannot be directly attributed to laboratory error.

"(2) For purposes of this section, the term "serious injury" shall mean—

"(A) a critical delay in diagnosis or causing the absence, delay, or discontinuation of appropriate medical treatment; or

"(B) an injury that—

"(i) is life threatening,

"(ii) results in permanent impairment of a body function or permanent damage to a body structure, or

"(iii) necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure.

"(3) Reports required under this section shall be submitted as follows:

"(A) An individual adverse event reports shall be submitted for the following events not later than—

"(i) 5 calendar days after an in vitro clinical test developer receives or otherwise becomes aware of information that reasonably suggests the adverse event involves a patient death; or

"(ii) 5 calendar days after an in vitro clinical test developer receives or otherwise becomes aware of information that reasonably suggests the event presents an imminent threat to public health.

"(B) Quarterly reports shall be submitted for all other adverse events and no later than the end of the quarter following the quarter in which the adverse event information was received by the in vitro clinical test developer.

[ ]**“SEC.587M. CORRECTIONS AND REMOVALS**

“(a) APPLICABILITY.

“(1) The Secretary shall amend part 806 of Title 21 of the Code of Federal Regulations (or any successor regulations) to apply to in vitro clinical tests. Until such amendment takes effect, such part shall be interpreted to apply to in vitro clinical tests.

“(2) The Secretary may by regulation require reporting of such corrections and removals as determined by the Secretary to be necessary to be reported to assure the analytical and clinical validity of in vitro clinical tests, and in addition, the safety of articles for taking or deriving specimens from the human body.

“(b) Reports of Removals and Corrections

(1) Each in vitro clinical test developer or importer shall report to the Secretary any correction or removal of an in vitro clinical test undertaken by such developer or importer if the removal or correction was undertaken –

(A) To reduce the risk to health posed by the in vitro clinical test, or

(B) To remedy a violation of this Act caused by the in vitro clinical test which may present a risk to health.

(2) The developer or importer shall submit any report required under this subsection to the Secretary within 10 business days of initiating such correction or removal.

(3) A developer or importer of an in vitro clinical test who undertakes a correction or removal of an IVCT which is not required to be reported under this subsection shall keep a record of such correction or removal.

(4) For purposes of this section, the terms “correction” and “removal” do not include routine servicing.

“SEC. 587N. RESTRICTED IN VITRO CLINICAL TESTS.

“(a) APPLICABILITY.

“(1) IN GENERAL - The Secretary, in issuing an approval, provisional approval, or precertification under sections [587_, _, or _] of an in vitro clinical test of a category described in paragraph (3) may require that such test be restricted to sale, distribution, or use upon such conditions as the Secretary may prescribe under paragraph (2).

“(2) CONDITIONS PRESCRIBED BY THE SECRETARY – The conditions prescribed by the Secretary under this paragraph, with respect to an in vitro clinical test described in paragraph (3), are those conditions which the Secretary determines due to the potentiality for harmful effect of such test (including any resulting absence, delay, or discontinuation of appropriate medical treatment), are necessary to assure the analytical or clinical validity of the test, or the safety of an article for taking or deriving specimens from the human body.

"(3) IN VITRO CLINICAL TESTS SUBJECT TO RESTRICTIONS - The restrictions authorized under this section may be applied by the Secretary to any high-risk in vitro clinical test, prescription home-use in vitro clinical test, direct-to-consumer in vitro clinical test, or over-the-counter in vitro clinical test.

"(4) PROMULGATION OF REGULATIONS.—In addition to imposing restrictions under paragraph (1), the Secretary may promulgate regulations restricting the sale, distribution, or use of any in vitro clinical test described in paragraph (3), based on such conditions as may be prescribed by the Secretary under paragraph (2) with respect to such test.

"(b) LABELING AND ADVERTISING OF A RESTRICTED IN VITRO CLINICAL TEST.

"(1) The label, labeling, and advertising of an= in vitro clinical test to which restrictions apply under subsection (a) shall bear such appropriate statements of the restrictions as the Secretary may prescribe in the approval, provisional approval, precertification, or regulation, as applicable.

"(2) Except in extraordinary circumstances, the Secretary shall not require prior approval of the content of any advertisement, and no advertisement of a restricted in vitro clinical test, published after the effective date of this section shall, with respect to the matters specified in this section 587[ ] or in orders or regulations issued hereunder, be subject to the provisions of sections 12 through 15 of the Federal Trade Commission Act (15 U.S.C. §§52-55). This subparagraph shall not be applicable to any printed matter which the Secretary determines to be labeling as defined in section 201(m).

"(c) An in vitro clinical test that was offered, sold, or distributed as a restricted device prior to the enactment date of this [subchapter/bill name] shall continue to comply with the applicable restrictions imposed under section 515 or section 520(e) until the effective date of restrictions issued under subsection (a).

"SEC. 587O. APPEALS. [*placeholder*]

"SEC. 587P. ACCREDITED PERSONS.

"(a) IN GENERAL.

"(1) REVIEW OF APPLICATIONS.

"(A) The Secretary may accredit persons for the purpose of reviewing applications for precertification and applications for premarket approval of an in vitro clinical test, and making recommendations to the Secretary with respect to such applications, subject to the requirements of this section.

"(B) The Secretary shall issue guidance on the factors that the Secretary will use in determining whether a test group or a scope of precertification is eligible for review by an accredited person.

"(C) In making a recommendation to the Secretary under this paragraph, an accredited person shall notify the Secretary in writing of the reasons for the recommendation concerning the application.

"(D) Not later than 90 days after the date on which the Secretary is notified of a recommendation under subparagraph (C) by an accredited person with respect to an application, the Secretary shall make a determination with respect to such application.

"(2) INSPECTIONS.

"(A) The Secretary may accredit persons for the purpose of conducting inspections under section 704 of in vitro clinical test developers and other persons required to register pursuant to section xxx, subject to the requirements of this section.

"(B) The Secretary shall issue guidance on the factors that the Secretary will use in determining whether an in vitro clinical test developer or other registered person is eligible for inspection by an accredited person.

"(C) Persons accredited to conduct inspections, when conducting such inspections, shall record in writing their specific observations and shall present their observations to the establishment's designated representative. Additionally, such accredited person shall prepare and submit to the Secretary an inspection report in a form and manner designated by the Secretary for conducting inspections, taking into consideration the goals of international harmonization of quality systems standards. Any official classification of the inspection shall be determined by the Secretary.

"(D) Any statement or representation made by an employee or agent of an establishment to a person accredited to conduct inspections shall be subject to section 1001 of title 18, United States Code.

"(E) Nothing in this section affects the authority of the Secretary to inspect any in vitro clinical test developer or other person registered under section XXX ..

"(b) ACCREDITATION.

"(1) ACCREDITATION PROGRAM.

"(A) The Secretary may provide for accreditation of persons to perform the duties specified under subsection (a) for some or all eligible in vitro clinical tests through programs administered by the Food and Drug Administration, by other non-Federal government agencies, or by qualified nongovernment organizations.

"(B) The Secretary shall issue guidance on the criteria that the Secretary will use to accredit or deny accreditation to a person who requests to perform any of the duties specified under subsection (a).

"(C) The Secretary shall not accredit or maintain accreditation for a person unless such person meets the minimum qualifications required under subsection (c).

"(D) The Secretary shall publish on the website of the Food and Drug Administration a list of persons who are accredited under this section. Such list shall be updated on at least a monthly basis. The list shall specify the particular activity or activities under this section for which the person is accredited.

"(2) ACCREDITATION PROCESS.

"(A) The Secretary shall issue guidance specifying the process for submitting a request for accreditation and reaccreditation under this section, including the form and content of information to be submitted in such a request.

"(B) The Secretary shall respond to a request for accreditation or reaccreditation within 90 days of the receipt of the request. The Secretary's response may be to accredit or reaccredit the person, to deny accreditation, or to request additional information in support of the request.

"(C) The accreditation of a person shall specify the particular activity or activities under subsection (a) for which such person is accredited, including if the activity is limited to certain eligible in vitro clinical tests.

"(D) The Secretary may audit the performance of persons accredited under this section for purposes of assuring that they continue to meet the published criteria for accreditation, and may modify the scope or particular activities for which a person is accredited if the Secretary determines that such person fails to meet one or more criteria for accreditation.

"(E) The Secretary may suspend or withdraw accreditation of any person accredited under this section, after providing notice and an opportunity for an informal hearing, when such person is substantially not in compliance with the requirements of this section or the published criteria for accreditation, or poses a threat to public health, or fails to act in a manner that is consistent with the purposes of this section.

(F) Accredited persons must be reaccredited at least every 2 years.

"(c) QUALIFICATIONS OF ACCREDITED PERSONS.

(1) An accredited person shall, at a minimum, meet the following requirements:

"(A) Such person may not be an employee of the Federal Government;

"(B) Such person shall not engage in the development of in vitro clinical tests and shall not be a person required to register under section XXX;

"(C) Such person shall not be owned or controlled by, and shall have no organizational, material or financial affiliation with, an in vitro clinical test developer or other person required to register under section XXX;

"(D) Such person shall be a legally constituted entity permitted to conduct the activities for which it seeks accreditation;

"(E) The operations of such person shall be in accordance with generally accepted professional and ethical business practices; and

"(F) Such person shall include in its request for accreditation a commitment to, at the time of accreditation and at any time it is performing activities pursuant to this section—

"(i) certify that the information reported to the Secretary accurately reflects the data or operations reviewed;

"(ii) limit work to that for which competence and capacity are available;

"(iii) treat information received or learned, records, reports, and recommendations as proprietary information of the person submitting such information; and

"(iv) in conducting the activities for which the person is accredited in respect to a particular in vitro clinical test, protect against the use of any employee or consultant who has a financial conflict of interest regarding that in vitro clinical test.

"(2) The Secretary may waive any requirements in subparagraphs (1)(A), (1)(B), or (1)(C) upon making a determination that such person has implemented other appropriate controls sufficient to ensure a competent and impartial review."

"(d) COMPENSATION OF ACCREDITED PERSONS.

"(1) Compensation of an accredited person who reviews an application for precertification or an application for premarket approval shall be determined by agreement between the accredited person and the person who engages the services of the accredited person, and shall be paid by the person who engages such services.

"(2) Compensation of an accredited person who is conducting an inspection under section 704 shall be determined by agreement between the accredited person and the person who engages the services of the accredited person, and shall be paid by the person who engages such services.

"(e) COOPERATIVE AGREEMENTS. The Secretary is authorized to enter into cooperative arrangements with officials of foreign countries to ensure that adequate and effective means are available for purposes of determining, from time to time, whether in vitro clinical tests intended for use in the United States by a person whose facility is located outside the United States shall be refused admission on any of the grounds set forth in section 801(a).

"SEC. 587Q. STANDARDS. [*placeholder*]

[placeholder for section authorizing FDA utilization of certain standards developed by non-governmental organizations in the review process]

"SEC. 587R. INVESTIGATIONAL USE

"(a) IN GENERAL. — Except as provided in subsection (c), an in vitro clinical test for investigational use shall be exempt from the requirements of this subchapter other than [sections

on appeals, preemption and applicability of FD&C Act].

"(b) The Secretary shall amend part 812 of Title 21 of the Code of Federal Regulations, or successor regulations, to apply as the Secretary deems appropriate to in vitro clinical tests and to implement the requirements in subsection (c). The Secretary shall amend parts 50, 54, and 56of Title 21 of the Code of Federal Regulations, or successor regulations, to apply as the Secretary deems appropriate to in vitro clinical tests. Until each such amendment takes effect, each such regulation shall be interpreted to apply to in vitro clinical tests.

"(c) APPLICATION FOR AN EXEMPTION.—

"(1) IN GENERAL.—

"(A)In the case of an in vitro clinical test the investigational use of which poses a significant risk, a sponsor of an investigation of such a test seeking an investigational use exemption shall submit to the Secretary an investigational use application with respect to the test in accordance with paragraphs (2) and (3). For purposes of this subparagraph, the term 'significant risk' means that the investigational use of the test—

"(i) is for a use of substantial importance in performing the activities described in section (ss)(1)(A) or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of an in vitro clinical test subject; or

"(ii) otherwise presents a potential for serious risk to the health, safety or welfare of a human subject of the in vitro clinical test.

"(B) In the case of an in vitro clinical test, the investigational use of which does not pose a significant risk—

"(i) the sponsor of such investigation shall comply with—

"(I) the requirements specified in paragraphs (3)(A), (3)(B), and (5)(A)(iii); and

"(II) such other requirements as the Secretary may determine to be necessary for the protection of the public health and safety, including the monitoring of investigations conducted with such test, the establishment and maintenance of records, or the submission to the Secretary of reports of data obtained as a result of the investigational use of the in vitro clinical test during the period covered by the exemption; and

"(ii) the sponsor may rely on any exception or exemption identified in paragraph (5)(B) or as established by the Secretary in regulations issued under subsection (b).b

"(2) APPLICATION CONTENTS.— An investigational use application shall be submitted in such time and manner and contain such information as the Secretary may require in regulation, and shall include assurances to the satisfaction of the Secretary that the sponsor involved shall, with respect to the in vitro clinical test that is the subject of the application—

"(A) establish and maintain any records relevant to such in vitro clinical test; and

"(B) submit to the Secretary reports of data obtained as a result of the investigational use of the in vitro clinical test during the period covered by the exemption that the Secretary reasonably determines will enable the Secretary—

"(i) to ensure compliance with the conditions for approval specified in paragraph (3);

"(ii) to review the progress of the investigation involved; and

"(iii) to evaluate the analytical validity and clinical validity of such test.

"(3) CONDITIONS OF APPROVAL.—An investigational use application with respect to an in vitro clinical test shall only be approved if each of the following conditions is met—

"(A) The Secretary finds that the risks to the subjects of the in vitro clinical test are outweighed by the anticipated benefits to the subjects and the importance of the knowledge to be gained, informed consent is adequate or waived, the investigation is scientifically sound, and there is no reason to believe that the in vitro clinical test as used is ineffective;

"(B) The proposed labeling for the in vitro clinical test involved clearly and conspicuously states 'For investigational use'; and

"(C) the sponsor submitting such application complies with the requirements of this section and such other requirements as the Secretary determines to be necessary for the protection of the public health and safety and requires in regulation.

"(4) COORDINATION WITH INVESTIGATIONAL NEW DRUG APPLICATIONS.—Any requirement for the submission of a report to the Secretary pursuant to an investigational new drug application involving an in vitro clinical test shall supersede the reporting requirement in paragraph (2)(B), but only to the extent the requirement with respect to the investigational new drug application is duplicative of the reporting requirement under such paragraph.

"(5) INVESTIGATION PLAN REQUIREMENTS.—

"(A) IN GENERAL.—With respect to a plan submitted under paragraph (3)(B), the sponsor submitting such plan shall—

"(i) in the case of such a plan submitted to an institutional review committee, promptly notify the Secretary of the approval or the suspension or termination of the approval of such plan by an institutional review committee;

"(ii) in the case of an in vitro clinical test to be distributed or otherwise made available to investigators for clinical testing, obtain, and submit to the Secretary, signed agreements from each of the individuals carrying out the investigation that is the subject of such plan that—

"(I) any testing under such plan involving human subjects will be under the supervision of such individual;

"(II) any testing under such plan will be conducted in compliance with the investigational plan and applicable regulations;

"(III) the individual will ensure that informed consent is obtained from each such human subject, except in cases specifically exempted pursuant to this section; and

"(IV) the individual will comply with additional investigator obligations as set forth in the final rule issued pursuant to subsection (b); and

"(iii) submit an assurance to the Secretary that informed consent will be obtained from each human subject (or the representative of such subject) of proposed clinical testing involving such in vitro clinical test, except in the following cases, for which informed consent is not required, subject to such other conditions as the Secretary may prescribe—

"(I) the proposed clinical testing poses no more than minimal risk to the human subject and includes appropriate safeguards to protect the rights, safety, and welfare of the human subject; or

"(II) the investigator conducting or supervising the proposed clinical testing determines (subject to subparagraph (B)(ii), with the concurrence of a licensed physician who is not involved in the testing of the human subject) in writing that—

"(aa) there exists a life-threatening situation involving the human subject of such testing which necessitates the use of such in vitro clinical test;

"(bb) it is not feasible to obtain informed consent from the subject; and

"(cc) there is not sufficient time to obtain such consent from a representative of such subject.

"(B) EXCEPTIONS.—

"(i) SIGNED AGREEMENTS NOT REQUIRED.—Subparagraph (A)(iii) shall not apply to the distribution of or other arrangements by a sponsor to make available an in vitro clinical test to an investigator that is employed by the sponsor.

"(ii) CONCURRENCE OF PHYSICIAN NOT REQUIRED.—The requirement to obtain the concurrence of a licensed physician or informed consent from the human subject's representative with respect to a determination under subparagraph (A)(iii)(II) shall not apply if—

"(I) immediate use of the in vitro clinical test in the investigation involved is required to save the life of the human subject; and

"(II) there is not sufficient time to obtain such concurrence.

"(iii) INFORMED CONSENT NOT REQUIRED WITH RESPECT TO CERTAIN SPECIMENS.— Notwithstanding subparagraph (A)(iii)(II), the informed consent of human subjects shall not be required with respect to clinical testing conducted as part of an investigation, if—

"(I) the clinical testing uses remnants of specimens collected for routine clinical care or analysis that would have been discarded, leftover specimens

that were previously collected for other research purposes, or specimens obtained from specimen repositories;

"(II) the identity of the subject of the specimen is not known to, and may not readily be ascertained by, the investigator or any other individual associated with the investigation, including the sponsor;

"(III) any clinical information that accompanies the specimens does not make the specimen source identifiable to the investigator or any other individual associated with the investigation, including the sponsor;

"(IV) the individuals caring for the human subjects as patients are different from, and do not share information about the patient with, the individuals conducting the investigation; and

"(V) the specimens are provided to the investigators without personally identifiable information and the supplier of the specimens has established policies and procedures to prevent the release of personally identifiable information.

"(6) VARIATION.—The requirements imposed under this subsection with respect to an investigational use application may vary based on—

"(A) the scope and duration of clinical testing to be conducted under investigation that is the subject of such application;

"(B) the number of human subjects that are to be involved in such testing;

"(C) the need to permit changes to be made in the in vitro clinical test involved during testing conducted in accordance with a plan required under paragraph (3)(B); or

"(D) whether the clinical testing of such in vitro clinical test is for the purpose of developing data to obtain approval to offer such test.

"(d) REVIEW OF APPLICATIONS.—

"(1) IN GENERAL.—The Secretary may issue an order approving an investigation as proposed, approving it with conditions or modifications, or disapproving it.

"(2) FAILURE TO ACT.—Unless the Secretary, not later than the date that is 30 calendar days after the date of the submission of an investigational use application that meets the requirements of subsection (c)(2), issues an order under subsection (d)(1) and notifies the sponsor submitting the application, the application shall be treated as approved as of such date without further action by the Secretary.

"(3) DISAPPROVAL.—The Secretary may disapprove an investigational use application submitted under this subsection if the Secretary determines that the investigation with respect to which the application is submitted does not conform to the requirements of subsection (c)(3). A notification of such disapproval submitted to the sponsor with respect to such an application shall contain the order of disapproval and a complete statement of the reasons for the Secretary's disapproval of the application.

"(e) WITHDRAWAL OF APPROVAL.—

"(1) IN GENERAL.—The Secretary may, by administrative order, withdraw the approval of an exemption granted under this subsection with respect to an in vitro clinical test, including an exemption granted based on the Secretary's failure to act pursuant to subsection (d)(2), if the Secretary determines that the test does not meet the applicable conditions under subsection (c)(3) for such approval.

"(2) OPPORTUNITY TO BE HEARD.—

"(A) IN GENERAL.—Subject to subparagraph (B), an order withdrawing the approval of an exemption granted under this subsection may be issued only after the Secretary provides the applicant or sponsor of the test with an opportunity for an informal hearing.

"(B) EXCEPTION.—An order referred to in subparagraph (A) with respect to an exemption granted under this subsection may be issued on a preliminary basis before the provision of an opportunity for an informal hearing if the Secretary determines that the continuation of testing under the exemption will result in an unreasonable risk to the public health. The Secretary will provide an opportunity for an informal hearing promptly following any preliminary action under this subparagraph.

"(f) CHANGES.—

"(1) IN GENERAL.—The amended regulations under subsection (b) shall provide, with respect to an in vitro clinical test for which an exemption under this subsection is in effect, procedures and conditions under which the changes to the test are allowed without the additional approval of an application for an exemption or the approval of a supplement to such an application. Such regulations shall provide that such a change may be made if—

"(A) the sponsor or applicant determines, on the basis of credible information (as defined by the Secretary) that the change meets the conditions specified in paragraph (2); and

"(B) the sponsor or applicant submits to the Secretary, not later than 5 calendar days after making the change, a notice of the change.

"(2) CONDITIONS.—The conditions specified in this paragraph are that—

"(A) in the case of developmental changes to an in vitro clinical test (including manufacturing changes), the changes—

"(i) do not constitute a significant change in design or in basic principles of operation;

"(ii) do not affect the rights, safety, or welfare of the human subjects (if any) involved in the investigation; and

"(iii) are made in response to information gathered during the course of an investigation; and

"(B) in the case of changes to clinical protocols applicable to the test, the changes do not affect—

"(i) the validity of data or information resulting from the completion of an

approved clinical protocol;

"(ii) the scientific soundness of a plan submitted under subsection (cc)(3)(B); or

"(iii) the rights, safety, or welfare of the human subjects (if any) involved in the investigation.

"(g) CLINICAL HOLD.—

"(1) IN GENERAL.—At any time, the Secretary may impose a clinical hold with respect to an investigation of an in vitro clinical test if the Secretary makes a determination described in paragraph (2). The Secretary shall, in imposing such clinical hold, specify the basis for the clinical hold, including the specific information available to the Secretary which served as the basis for such clinical hold, and confirm such determination in writing. The applicant or sponsor may immediately appeal any such determination pursuant to [section XX appeals].

"(2) DETERMINATION.—For purposes of paragraph (1), a determination described in this subparagraph with respect to a clinical hold is a determination that—

(A) the in vitro clinical test involved represents an unreasonable risk to the safety of the persons who are the subjects of the clinical investigation, taking into account the qualifications of the clinical investigators, information about the in vitro clinical test, the design of the clinical investigation, the condition for which the in vitro clinical test is to be investigated, and the health status of the subjects involved; or

(B) the clinical hold should be issued for such other reasons as the Secretary may by regulation establish.

(C) Any written request to the Secretary from the sponsor of an investigation that a clinical hold be removed shall receive a decision, in writing and specifying the reasons therefor, within 30 days after receipt of such request. Any such request shall include sufficient information to support the removal of such clinical hold.

"SEC. 587S. EMERGENCY USE AUTHORIZATION.

"An in vitro clinical test may be authorized for use in emergency, and used, held, and developed for such use, pursuant to Sections 564, 564A, 564B, and 564C.

"SEC. 587T. COLLABORATIVE COMMUNITIES FOR IN VITRO CLINICAL TESTS

"(a) IN GENERAL.--

"(1) The Secretary may initiate, establish and participate in collaborative communities of public and private participants that may provide recommendations

and other advice to the Secretary on the development and regulation of in vitro clinical tests.

"(2) A collaborative community under this section shall have broad representation of interested private and public-sector stakeholder communities and may include patients, care partners, academics, healthcare professionals, healthcare systems, payers, federal and state agencies, international regulatory bodies, industry, or other interested entities or communities.

"(b) RECOMMENDATIONS.— A collaborative community may make recommendations to the Secretary on matters including—

"(1) Mitigating measures for in vitro clinical tests;

"(2) Standards development activities and performance standards for in vitro clinical tests;

"(3) Scientific and clinical evidence to support new claims for in vitro clinical tests;

"(4) New technologies and methodologies for in vitro clinical tests;

"(5) Stakeholder engagement;

"(6) New approaches and solutions to multifaceted problems involving diverse stakeholders; and

"(7) Development of effective policies and processes.

"(c) USE BY SECRETARY.-- The Secretary may adopt one or more recommendations made under subsection (b), or otherwise incorporate the feedback from collaborative communities, in its application of its authorities under this [subchapter/bill name] to one or more in vitro clinical tests or a group of in vitro clinical tests, as appropriate.

"(d) TRANSPARENCY - The Secretary shall:

"(1) Publish on the internet website of the Food and Drug Administration matters for which it is seeking comments or recommendations;

"(2) Maintain a list of Collaborative Communities recognized by the Secretary and make this list available on the internet website of the Food and Drug Administration; and

"(3) Post on the internet website of the Food and Drug Administration at least once every year a report on the recommendations it has adopted from Collaborative Communities.

"(e) The Federal Advisory Committee Act in the appendix to title 5 shall not apply to collaborative communities established and used in accordance with this section.

"SEC. 587U. CTIS. [*placeholder*]

"SEC. 587V. PREEMPTION. [*placeholder*]

"SEC. 587W. USER FEES. [*placeholder*]

"SEC. 4. TRANSITION.

(a) FUNDING. – For the purposes of carrying out this Act, there is authorized to be appropriated [$X MILLION] for fiscal year X.

(b) IMPLEMENTATION — The amendments made by this Act shall take effect on DATE X, except that the Secretary is authorized to take such actions, and expend such funds, as the Secretary deems necessary to prepare for this Act to take effect and to ensure an orderly transition.

(c) APPLICATION OF DEVICE AUTHORITIES TO IN VITRO CLINICAL TESTS UNTIL AND AFTER EFFECTIVE DATE OF THIS ACT. — Except as provided in subsection (d), for any product or test that is within the definition of in vitro clinical test as established under the amendments by this Act, the following authorities shall apply:

(1) Any such product or test that was offered, sold, or distributed prior to the enactment date of this Act, except for those addressed in paragraph (d), shall continue to comply with the applicable device provisions of the Federal Food, Drug, and Cosmetic Act and the Public Health Service Act until the effective date of this Act.

(2) Before any such product or test is first offered, sold, or distributed after the enactment date but prior to the effective date of this Act, such product or test shall comply with the applicable device provisions of the Federal Food, Drug, and Cosmetic Act and the Public Health Service Act, except that a product or test which is the same type of product or test referenced in subsection (d) shall likewise be subject to the provisions of that subsection.

(3) For any such product or test that has a submission for marketing authorization under section 515, clearance under section 510(k), authorization under 513(f)(2), approval under section 520(m), or emergency use authorization under section 564 of the Federal Food, Drug, and Cosmetic Act or approval under the Public Health Service Act pending on the effective date of this Act, the Secretary is authorized to review and take action on such submission after the effective date of this Act according to the statutory provision under which such submission for marketing authorization was submitted.

(d) APPLICATION OF AUTHORITIES TO GRANDFATHERED AND TRANSITIONAL IN VITRO CLINICAL TESTS.–

(1) For purposes of this subsection, a Transitional In Vitro Clinical Test is an in vitro clinical test that was developed by a laboratory certified by the Secretary under section 263a of title 42 of the United States Code that meets the requirements for performing high-complexity testing for use only within that certified laboratory and that does not have an approval under section 515, a clearance under section 510(k), an authorization under 513(f)(2), an approval under section 520(m), or an emergency use authorization under section 564 of the Federal Food, Drug, and Cosmetic Act or an approved application under the Public Health Service Act, and is first offered for clinical use in the

period that is within the 90 days preceding the enactment date and up to the effective date of this Act.

(2) An in vitro clinical test that was first offered for clinical use prior to the enactment date of this Act and that meets the criteria for a grandfathered test as set forth in section 587A(c)(2) of the Federal Food, Drug, and Cosmetic Act as added by this Act may continue to be offered for clinical use until the effective date of this Act, except that the Secretary of Health and Human Services retains authority to enforce the device provisions of the Federal Food, Drug, and Cosmetic Act and the Public Health Service Act for any specific product or test or any type of product or test as the Secretary determines necessary to protect the public from a serious risk to health. Such in vitro clinical test shall be subject to the applicable provisions of this Act as of the effective date of this Act.

(3) A transitional in vitro clinical test may continue to be offered for clinical use until the effective date of this Act, except that the Secretary of Health and Human Services retains authority to enforce the device provisions of the Federal Food, Drug, and Cosmetic Act and the Public Health Service Act for any specific product or test or any type of product or test as the Secretary determines necessary to protect the public from a serious risk to health. Such in vitro clinical test shall be subject to the provisions of this Act as of the effective date of this Act.

(4) A transitional in vitro clinical test under paragraph (1) that is the subject of an application for premarket review or precertification that is submitted on the effective date or within [ ] days of the effective date of this Act may continue to be offered, sold, or distributed until completion of the Secretary's review of the premarket application or precertification application.

(e) CONVERSION.–

(1) Any in vitro clinical test as defined by [definitions section] with a premarket approval, a clearance under section 510(k), an authorized de novo under section 513(f), or a BLA under the Public Health Service Act is deemed to have an approved application under section [premarket review] after the effective date of this Act.

(2) Any in vitro clinical test that has an approved investigational device exemption under section 520(g) is deemed to have an approved investigational use under section 587Q after the effective date of this Act.

(f) PLATFORMS.– A test platform that was purchased prior to the enactment date of this Act and was not cleared, authorized, or approved by the Food and Drug Administration at the time of purchase may continue to be used by the purchaser to develop and introduce into interstate commerce an in vitro clinical test during the period up to five years after the enactment date of this Act. Beginning five years after the enactment date of this Act, any new in vitro clinical test that is developed and introduced into interstate commerce in accordance must be based on a test platform that complies with the requirements of this Act.

(g) These transition provisions apply notwithstanding the provisions of Section 587A(a)(1)(C).

“SEC. 5. GENERAL APPLICABILITY. The Federal Food, Drug, and Cosmetic Act (21 U.S.C. § 301 et seq.) is amended—

[Placeholder for provision which includes IVCTs in all the necessary violative, adulteration, misbranding and other relevant sections of the FDCA and PHSA (e.g., section 319F-3, etc.), or new language for these sections where necessary].

“SEC. 6. ANTIMICROBIAL SUSCEPTIBILITY TESTS.

“(a) Section 511A of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. § 360a-2) is amended—

(1) by inserting in subparagraph (a)(1)(C) after the words “section 515” the words “clear, approve, or exempt under [Subchapter J ref. 587A sections] and before “antimicrobial susceptibility…” and
(2) By replacing “testing devices” with “tests.”
(3) by inserting “or in vitro clinical test” after “device” in both instances in (c)(5)
(4) by inserting “in vitro clinical tests” after “susceptibility” in (e)
(5) by striking “and” in (e), inserting “and” after “515” and then inserting [reference to in vitro clinical test IPA approval provision]
(6) by replacing “device” with “in vitro clinical test” in each occurrence in (e)
(7) by striking (e)(2)(C) and replacing with “(C) The antimicrobial susceptibility test in vitro clinical test meets all other requirements to be approved under [insert ref. to in vitro clinical test IPA provision] or exempted from premarket review under [add ref to applicable precert provision] of this title.”
(8) by striking (f)(1) and replacing it with “The term “antimicrobial susceptibility test in vitro clinical test” means an in vitro clinical test that utilizes susceptibility test interpretive criteria to determine and report the in vitro susceptibility of certain microorganisms to a drug (or drugs).”
(9) by striking (g)(2) and replacing it with “with respect to approving in vitro clinical tests under section [add ref. to in vitro clinical test IPA approval provision] or exempting in vitro clinical tests from premarket review under [add ref to applicable precert section] of this title — “
(10) by replacing “device” with “in vitro clinical test” and “antimicrobial susceptibility testing device” with “antimicrobial susceptibility in vitro clinical test” in (g)(2)(A).

“SEC. 7. COMBINATION PRODUCTS.

(a) Section 503(g) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 353(g)) is amended—

(1) in subparagraph (1)(A) by inserting “except for a combination product constituted of a device and an in vitro clinical test,” after “agency center,” and by inserting “in vitro clinical test” before “or biological product.”
(2) in subparagraph (1)(D) by inserting “except for a combination product constituted of a device and an in vitro clinical test. For other combination products,” before “if the Secretary…”
(3) in subparagraph (1)(D)(ii) by inserting “or in vitro clinical test” after “device” and “and

in vitro clinical tests" before "shall"

(4) in subparagraph (3) by adding [reference to the relevant standard for in vitro clinical tests] before "for the approved constituent part…"

(5) in subparagraphs (4)(A), 4(B), and 5(A), by adding "[cites to in vitro clinical test IPA provision]" to the list of [sections]

(6) in subparagraph (7) by adding "[reference to the relevant standard for in vitro clinical tests]" after "substantial equivalence"

(7) in subparagraph (8) by adding "This paragraph shall not apply to a combination product constituted of a device and an in vitro clinical test"

(8) in subparagraph (9)(C)(i) by striking "or" before "520(g) and adding "or [cite to IPA approval provision]" at the end

(9) in subparagraph (9)(D) by striking "or" before "520" and adding "or [cite to in vitro clinical test IPA provision]" before "of this Act…"

(b) Section 563 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360bbb-2) is amended --

(1) in subsection (a) by inserting "in vitro clinical test," after "device," and by inserting ", except for a combination product constituted of a device and an in vitro clinical test," before "respecting the component…"

(2) in subsection (b) by inserting "except for a combination product constituted of a device and an in vitro clinical test" before "the component of the…"

(3) in subsection (c) by inserting "except for a combination product constituted of a device and an in vitro clinical test" before "the component of the…"

"SEC. 8. LIST OF ADULTERATION, MISBRANDING, AND PROHIBITED ACTS/GENERAL ENFORCEMENT PROVISIONS [*placeholder*]

Blockchain in Healthcare

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WHITE PAPER

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Blockchain for Business

As the interest in blockchain technology grows, companies will be confronted with numerous decisions, challenges, and legal issues pertaining to its adoption. Relevant matters include the overall design and control of blockchain systems, potential liability for use (or misuse) of the data they contain, and the consequences flowing from being able to track data and transactions on an immutable, near–real time basis.

This Jones Day *White Paper*, "Blockchain for Business," considers common use cases for different business sectors and focuses on the basic legal issues relevant to adoption of blockchain technology across 12 major jurisdictions.

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BLOCKCHAIN FOR BUSINESS

Organizations across every sector and of every size and complexity are being told that blockchain technology will revolutionize their business—both for better (by reducing costs/transaction times or increasing security) and for worse (by disrupting or even extinguishing entire business lines that can be replaced by this new technology).

In August 2016, the advisory firm Gartner suggested that blockchain technologies had reached "the Peak of Inflated Expectations" in its respected Hype Cycle for emerging technologies. By August 2018, blockchain technologies had transitioned into "the Trough of Disillusionment," meaning that initial interest has waned as some implementations fail to deliver promised efficiencies. However, the technology is now expected to reach maturity in as a little as five to 10 years. At the same time, blockchain implementations are already being used to conduct everyday business and in certain areas are delivering significant market changes in process.

The great strength of blockchain technology is its flexibility and adaptability to a range of business uses. However, this flexibility also presents a significant challenge to any organization wanting to implement the technology for the first time.

Key issues to consider are:

- The overall design and control of the system;
- Potential liability for use (or misuse) of the data contained on it;
- The consequences that flow from being able to track data and transactions on an immutable, near–real time basis.

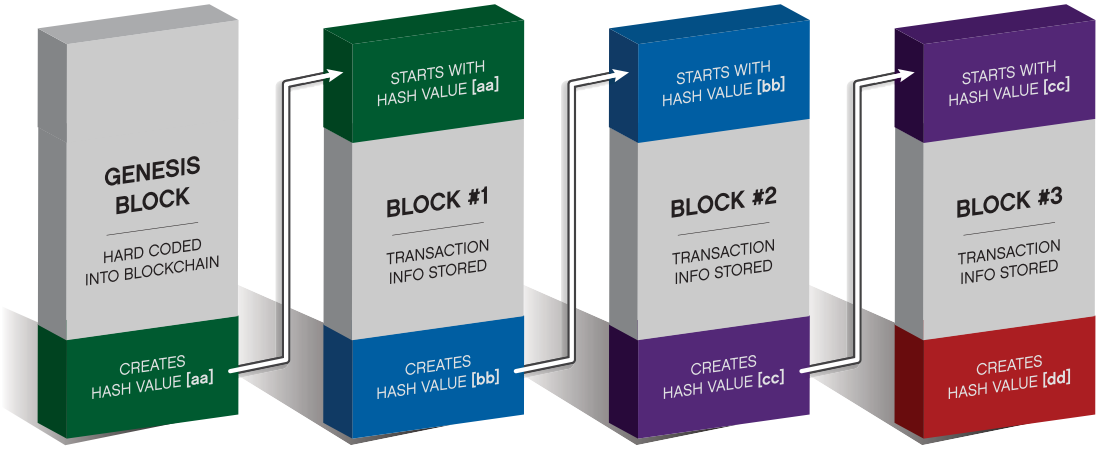
There are other challenges—not least, how to integrate blockchain ledgers into existing systems and manage data transfer between those systems in compliance with law and regulation.

As the level of interest in blockchain technology grows, Jones Day's group of involved lawyers has prepared this *White Paper*, "Blockchain for Business." We consider common use cases for different business sectors and focus on the basic legal issues relevant to adoption of blockchain technologies in the United States, United Kingdom, France, Germany, Italy, the Netherlands, Spain, the People's Republic of China, Hong Kong, Singapore, Japan, and Australia. We also discuss the underlying technology and explain why so many organizations are looking to test and adopt blockchain in their daily business.

WHAT IS BLOCKCHAIN TECHNOLOGY?

Blockchain is a technology for storing, tracking and processing information.[1] At its simplest, a blockchain is a digital database of transactions.

As represented in the diagram below, each transaction is stored in a block of data that is securely linked to the blocks containing previous and subsequent transactions (hence "blockchain"). The secure link between blocks makes it simple to track and audit the validity of the data, making blockchains much more difficult to hack or falsify.



1 The technology is interchangeably referred to as blockchain, block chain, shared ledger technology, distributed ledger technology, and DLT. We use "blockchain" in this *White Paper*.

Blockchain technology is also capable of running "smart contracts." A smart contract is a piece of computer code using standard prewritten logic (e.g., *if* that happens, *then this* is the outcome). When a smart contract is stored on a blockchain, it can be made self-executing and self-enforcing. In other words, when the *if* condition in the smart contract is fulfilled, the *then this* transaction outcome is automatically put into place by the blockchain, without the need for any human intervention or approval.

We discuss the technology behind blockchain, including smart contracts, in the Appendix to this *White Paper*.

COMMON USE CASES FOR BLOCKCHAIN TECHNOLOGY

There is a wide range of possible uses for blockchain, particularly in relation to financial transactions. We highlight some common implementations in use or in development across a range of sectors.

Banks and Financial Institutions

The majority of the early discussion on blockchain implementations focused on banking and financial services—both because the technology has the ability to significantly disrupt the way that existing financial transactions are carried out, and also because it would allow banks to carry out current transactions more quickly and efficiently.

At the same time, banking and financial services are highly regulated industries, requiring potential users of blockchain technologies to manage the risks carefully, as well as undertake significant engagement with regulators as part of implementation.

Trading, Clearing, and Settlement. In the near term, the most active use case for blockchain technology in banking will be in trading, clearing, and settlement—i.e., the process of turning an executed transaction into value by transferring an asset in exchange for payment by a settlement date. Currently, clearing and settlement across a range of financial assets requires intermediary organizations that take on the role of processing and reconciling instructions and orders between transacting parties. Trade settlement is often done on a T+2, T+3 or T+5 basis, meaning that the buyer and seller are exposed to the risk of a significant market change in that 2, 3 or 5 day period.

Blockchain technologies offer the possibility of quicker and cheaper clearing and settlement using the traditional infrastructure, but have also brought a host of new market participants which offer settlement of transactions without using traditional intermediaries.

The use of blockchain technology for trading, clearing, and settlement has steadily gained traction. In December 2017, the Australian Securities Exchange announced that it was replacing its clearing and settlement system, "Chess," with a blockchain-based system developed by Digital Asset Holdings. The target go-live date is currently set between March and April 2021. Likewise, the Canadian Securities Exchange announced in February 2018 plans to apply for regulatory recognition of a new clearinghouse system that is based on blockchain that will enable securities to be traded, cleared, and settled in real–time.

Potential Advantages of Blockchain: Quicker transaction times, reduced third-party costs, reduced collateral obligations on participants, reduced risk of information inconsistency/need for reconciliation between parties.

Loan Origination and Securitization. Efforts are also underway to apply blockchain technology to loan origination and securitization. The current process involves multiple market participants with extensive manual inputs. Originators, sponsors/issuers, servicers, rating agencies, trustees, investors, and regulators evaluate and track data and create various models that result in significant duplication of work and gaps that could create commercial and legal risks. In addition, originators could open their portfolios for investors to meet their risk appetite or to combine claims from different originators according to their risk profiles. The Structured Finance Industry Group and Chamber of Digital Commerce have partnered together to advance the use of blockchain technology in the loan origination and securitization markets and commissioned Deloitte to issue a white paper to provide an overview. There are also various initiatives looking at the individual steps along the value chain to identify specific elements that are suitable use cases for blockchain and/or smart contract technology either at the origination level (including Know Your

Customer ("KYC") requests) and/or at the note level to automate these processes.

Potential Advantages of Blockchain: Lower costs, enhanced transparency, reduced risk of errors and fraud. Permits originators to move away from single large transactions and move toward more frequent granular and automated transactions (i.e., smart contracts) in accordance with their funding needs. Can open up funding opportunities for new market entrants, particularly in countries where funding via capital markets has not yet reached full potential, for example in parts of Africa.

Know Your Customer. KYC requests are a significant cause of delay to consumer, retail, and commercial banking transactions. In addition to the time that KYC takes, current processes require duplication of effort between banks and other third-party institutions and have significant cost implications. If a customer can provide its KYC information to a blockchain in a form that a group of banks agrees is acceptable to them all (perhaps with a level of third-party verification), each bank could rely on the ledger as the basis for its KYC rather than having to conduct its own checks. The customer only has to supply or update the information only once and can have confidence that the information is disclosed only once for the purposes of checking and verification. However, this use case raises another issue that banks will need to consider carefully—the safety and security of information stored on a blockchain. Although the very nature of a distributed ledger makes it significantly harder to "hack," secure storage of customer data, particularly consumer data, will be a key issue for regulators.

For example, on October 3, 2017, in Singapore, the Infocomm Media Development Authority of Singapore announced that it has collaborated with a number of major banks, including HSBC, Mitsubishi UFJ Financial Group, and OCBC Bank, to complete the ASEAN region's first KYC blockchain proof-of-concept. Using a DLT, the KYC blockchain will allow information to be maintained and validated among participating banks.

Potential Advantages of Blockchain: Better customer experience, greater access to financial services for consumers and other users, lower costs, enhanced transparency and auditability for banks, better security, and reduction in fraud risk, enhanced compliance with KYC obligations.

Payments. One of the most high-profile, active examples of blockchain technology is the Bitcoin cryptocurrency system, which can be used to make or receive payments to third parties. While it is unlikely that any business-to-business payment blockchain will replicate the way that bitcoin works (e.g., it will not be acceptable for big businesses to allow users of a payment system to remain anonymous), the transfer of value always has been complicated and slow, and the process has not changed significantly since the early 1980s. This is particularly true for cross-border payments. Organizations such as SWIFT and R3 (a banking industry consortium) are developing payment systems using blockchain technologies that will allow bank-to-bank, business-to-bank, and business-to-business payments and promise quicker and cheaper transactions. Just as an example, a blockchain payment system could allow a bank to process payments continuously, 24 hours a day. However, a significant issue that those projects will need to address is that of scalability—no blockchain has yet been able to process billions of transactions a second in the way that current bank payment systems can.

One potential example that could help address these issues is "Money Tap," which is a payment app created by the blockchain firm Ripple. The application allows transactions to be settled instantly. It was initially made available with three banks: SBI Net Sumishin Bank, Suruga Bank, and Resona Bank, but was then accessible to a broader consortium.

Potential Advantages of Blockchain: Quicker and cheaper transactions for customers, reduced costs and liquidity obligations on payment processors, greater transparency and traceability of payments, reduction in fraud.

Corporates

Trade Finance. One area of business that is likely to be transformed by blockchain technologies is trade finance—the historic process for which traces its roots back to 16th-century European merchants. Current processes normally require banks to issue letters of credit or other forms of finance against shipped goods (which can be hard for smaller businesses to obtain at reasonable cost), but that can also lead to long delays in payment for the seller or exporter.

The ability of a blockchain to track real-world assets in real time and release payments automatically (via smart contracts)

on delivery of goods would make it easier for companies to agree to export goods and have confidence in receiving payment, as well as giving the buyer confidence in delivery and reduce the risk of fraud where goods are stolen or substituted during the transport process.

In October 2016, Wells Fargo and Commonwealth Bank of Australia used a blockchain to process a shipment of cotton from the United States to China for the first time, including using a smart contract to execute the terms of the sale, transfer the ownership of the goods on receipt, and initiate payment for the goods to the seller. In 2018, interest in blockchain-based trade finance solutions continued to grow.

In July 2018, Hong Kong's de facto central bank announced that would go live with a blockchain-backed trade platform that will link 21 banks, including HSBC, an initiative that marks one of the first and largest government-led blockchain projects aimed at upgrading trade finance. Likewise, HSBC announced in May 2018 that it had executed the world's first commercially viable trade finance transaction using blockchain. Deutsche Bank and Rabobank have joined forces to launch a similar businesses.

Potential Advantages of Blockchain: Transparency and visibility of the transaction at every stage of the process, reduced costs, reduction in fraud and disputes over transactions, greater access to cost-effective trade finance for smaller businesses.

Supply-Chain Management. In a similar way, blockchain technology will allow companies to securely and transparently track the permanent history of products they produce from manufacture to sale, including any third-party components used.

A blockchain could be used to record the nature, quantity, and transfer of assets; track purchase orders, receipts, and shipment notifications; assign certifications or record properties of physical products, as well as link physical goods to serial numbers, bar codes, or RFID tags. It is even being used by some companies to monitor and record the conditions in which perishable goods are stored as they move through the transport process, giving the end consumer "farm to table" visibility on the food items they are purchasing.

Potential Advantages of Blockchain: Significant opportunities to reduce fraud, introduce manufacturing efficiencies, improve traceability of products, and improve the end-customer experience. An example is the successful start-up Everledger, which has uploaded unique identifying data on more than a million individual diamonds to a blockchain ledger system to reduce crime and insurance fraud and to help the jewelry industry comply with regulations barring "blood diamond" products.

Intellectual Property

Blockchain technology is already making it easier for people and companies to protect their intellectual property. Several start-up companies enable content owners to create a permanent record of their work in a public database based on blockchain technology. This technology provides a time-stamped proof of creation that many content owners lack because they do not immediately register copyright in their work. Existing applications of the technology will allow people to authenticate artistic works and monitor the transfer of ownership between sellers and buyers. Content owners can also use the technology to publish their works, manage licensing options and control their digital rights.

Potential Advantages of Blockchain: Enables content creators to prove ownership and control distribution of work, verify authenticity, and resolve problems of attribution

Insurance

A number of the use cases discussed above are relevant to the commercial insurance industry. Blockchain technologies also have the potential to change the way that personal insurance products are written and managed. Blockchain-based personal identity schemes could be used by insurance companies to validate claims and make payments to people without needing to undertake significant adjusting activity. Many commentators and insurance companies have focused on the life insurance industry in particular, where registration and confirmation of death can be a time-consuming and upsetting process for families when they are at their most vulnerable. Blockchain-based insurance systems allied with smart contracts could enable claims to be processed automatically on formal notification of death, with payments being made within days (rather than months) to the beneficiaries. These features can also be applied to casualty insurance, such as car insurance.

Potential Advantages of Blockchain: Reduced costs, better customer experience, reduced risk of fraud.

LEGAL ISSUES TO CONSIDER WHEN IMPLEMENTING BLOCKCHAIN TECHNOLOGY

The precise legal issues that arise on any implementation of blockchain technology will vary, depending on the sector, product, and use case. A manufacturer using blockchain to track third-party components incorporated into its products will have a particular focus on product liability issues, whereas a bank using blockchain to process customer payments will be highly focused on consumer regulation and data security. However, most blockchain implementations require consideration of issues in five key legal areas. We set these out below together with some of the critical considerations in each category.

Jurisdiction

- Governing law of transaction
- Place of performance of transaction
- Nature of asset being transferred

Liability

- Responsibility for blockchain performance
- Technology or design failure
- Enforceability of transaction

Applicable Law/Regulation

- Ensure blockchain enforces existing laws/regulations which may apply to asset being transferred or type of transaction
- Ensure participants are limited to those who can legally transact

Cybersecurity and Data Privacy

- Ensure compliance with applicable laws and regulations
- Manage data transfer issues across borders
- Consider issues of data privacy, reporting and risk of breach

Intellectual Property

- Patent acquisition and liability
- Open Source usage

JURISDICTIONAL OVERVIEW

In this section, we focus on some of the central legal issues relevant to the adoption of blockchain technologies in different countries around the world.

As can be seen from this *White Paper*, blockchain, by its nature, is capable of operating across jurisdictions and without necessarily incorporating the traditional building blocks of contracts, such as choice of jurisdiction and governing law.

The ability to attach and transfer the ownership and value of real-world assets using a blockchain is a further challenge to traditional legal concepts in some countries—for example, some European countries require certain transaction documents to be notarized before becoming effective—where changes in law may be necessary for the technologies to become fully effective.

There are also more fundamental legal questions that will need to be addressed by treaties, national legislation, and/or courts—including what is the correct categorization of an asset that exists only on a blockchain (such as a bitcoin), given that there is no obvious way of taking physical possession of that asset unless and until it is transferred into a fiat currency. It seems likely that a number of these issues initially will come up in the context of tax/revenue cases, such as the *Hedqvist* case before the Court of Justice of the European Union.

These questions are complex and beyond the scope of this introductory *White Paper*, but we set out below an overview of the approach to blockchain technologies in key countries that are focusing on developing legal infrastructure to support them.

UNITED STATES OF AMERICA

OVERVIEW

The highly fragmented regulatory system in the United States, which involves both federal and state legislation and regulation, administered by a broad array of specialized governmental agencies, has produced varying levels of engagement with blockchain technology and often disparate regulatory responses. As a result, the United States regulatory landscape has created substantial uncertainty for businesses seeking to employ novel applications of blockchain technology. The result is a poorly defined yet complex framework marked by stringent regulatory requirements lacking specificity as to their application to blockchain technology.

Initial engagement on both a state and federal level largely has focused on virtual currency, rather than broader applications of blockchain technology. As a result, the regulation by U.S. banking regulators of currency transmission is more advanced than other applications of blockchain technology—although, here too, U.S. decentralized regulation has resulted in a complicated state-by-state licensing process in addition to compliance with guidance from federal agencies, such as FinCEN (The Financial Crimes Enforcement Network).

Outside of currency transmission regulation, federal lawmakers and regulators have been slow to engage with issues arising from new blockchain technologies. At a legislative level, only tentative steps have been taken to engage blockchain technology—generally in the form of legislative panels and study groups. Key U.S. regulators, including the CFTC, SEC, and the Financial Industry Regulatory Authority ("FINRA"), recently have initiated dialogue with market participants and signaled a desire to encourage innovation. However, often anachronistic regulatory frameworks—adopted in a different technological era—substantially limit regulatory flexibility for blockchain innovators. At the same time, several U.S. states have undertaken various legislative initiatives with respect to targeted aspects or applications of blockchain technology. As a result, although there continues to be a strong U.S. fintech sector, the United States has struggled to compete effectively with jurisdictions offering greater legal and regulatory coherence, certainty, and flexibility.

In addition, any use of blockchain technology must navigate a wide-spanning assortment of additional legal requirements in areas such as data protection, consumer protection, anti-money laundering, and sanctions, as well as meeting general requirements for large companies and regulated entities to have adequate systems and processes to manage risk in their businesses.

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LEGISLATION/ REGULATION

At the federal level, only tentative steps have been taken to engage directly in legislating blockchain technology, generally through requests for guidance and the formation of study groups (such as the Congressional Blockchain Caucus) dedicated to blockchain technology. To date, no specific legislative proposals principally addressing blockchain technology or its applications have been adopted.

In contrast, over the past several years, state regulators have gradually established regulatory positions, at least in some targeted areas, with respect to blockchain technology. State-by-state regulation initially targeted money transmission licensing requirements. For instance, New York's "BitLicense," which has been granted to six firms and covers a broad range of virtual currency activities, permits license holders to engage in:

- Virtual currency transmission;
- Storing, holding, or maintaining custody or control of virtual currency on behalf of others;
- Buying and selling virtual currency as a customer business;
- Performing exchange services as a customer business; and
- Controlling, administering, or issuing a virtual currency.

In addition, states such as New York are issuing limited purpose trust company charters to companies operating virtual currency transmission storing, holding, or maintaining custody or control of virtual currency on behalf of others buying and selling virtual currency as a customer business.

In addition, U.S. states have begun extending legislative proposals to other aspects of blockchain technology, particularly in the area of corporate governance. For example:

- Vermont permits the use of blockchain technology to validate the "identity, participation, and status in the formation, management, record keeping, and governance of any person." Also, digital records registered in blockchain are self-authenticating under the Vermont's evidentiary rules, if the records are accompanied by a sworn, written declaration. Vermont also created studies for expanding the use and promotion of blockchain technology, enabled the creation of blockchain-based limited liability companies, and created a study for the potential use of blockchain technology in government records.
- Delaware allows any of a corporation's or limited partnership's records, including its stock ledger, to be kept by means of "any information storage device, method, or one or more electronic networks or databases (including one or more distributed electronic networks or databases)," provided that the records can be converted into paper form in a reasonable period of time. Registration of beneficial interests in statutory trusts may be evidenced through blockchain technology. The Delaware Statutory Trust Act has been amended to provide that registration of a beneficial interest in a statutory trust may be evidenced electronically through blockchain technology.
- Arizona expressly permits signatures secured through blockchain technology to serve as valid electronic signatures and establishes smart contracts as legal, enforceable contracts. Arizona also prohibits regulating "the act of running a node on blockchain technology in a person's residence" by any city, town, or county.
- Wyoming provides an exemption for virtual currency used within Wyoming from money transmitter laws and regulations. Developers, sellers, and facilitators of the exchange of an open utility token are also exempt from state securities and money transmission laws. Virtual currency is also exempt from property taxation. Wyoming provides for the maintenance of corporate records of Wyoming entities via blockchain as long as electronic keys, network signatures, and digital receipts are used.
- California provides that, if a law requires a record to in writing, or if a law requires a signature, an electronic record or signature satisfies the Uniform Electronic Transactions Act. California is also organizing a blockchain working group designed to assess the use of blockchain technology in California. California is also considering authorizing corporations to maintain stockholder records on or by means of blockchain technology.
- Tennessee recognizes the legal authority to use blockchain technology and smart contracts in conducting electronic transactions.

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LEGISLATION/ REGULATION

Federal regulatory agencies have taken a variety of steps:

- The OCC—the U.S. regulator responsible for chartering and supervising national banks and federal savings associations—has announced a financial innovation initiative pursuant to which it will accept applications for special purpose national bank charters from fintech companies, which would preempt these companies from many state-level regulatory requirements (*see* Jones Day Commentary, "Fintech Banks—Comptroller of the Currency Proposes New Special Purpose Charter" and "The OCC's Responsible Innovation Framework and Fintech Bank Charters—Latest Developments"). However, this initiative has been subject to continual legal challenges by state regulators.
- The CFTC, which has been among the federal agencies most supportive of fintech innovation, opened in May 2017 LabCFTC to promote fintech innovation and fair competition by making the CFTC more accessible to fintech innovators and serving as a platform to inform the CFTC's understanding of new technologies. In July 2017, it granted the first swap execution facility registration to an entity offering clearing services and a trading facility for options based on digital currency. In May 2018, it released new guidance for clearinghouses and exchanges planning to list cryptocurrency-related derivatives products.
- FINRA, which regulates U.S. brokers and dealers, published a discussion paper in January 2017 opening a dialogue with market participants and seeking comment on the implementation and regulation of applications employing blockchain technology. In June 2017, FINRA announced that it has established an Innovation Outreach Initiative to foster an ongoing dialogue with the securities industry that will help FINRA better understand financial technology innovations and their impact on the industry. In July 2018, FINRA issued a regulatory notice encouraging firms to notify FINRA if they engage in activities related to blockchain and digital assets, and it issued a special notice requesting comment on financial technology innovation in the broker-dealer industry.
- The SEC—the U.S. securities regulator—issued in July 2017 an Investigative Report cautioning market pa rticipants in initial coin offerings ("ICOs") to carefully evaluate whether the offered digital assets constitute securities that are subject to the U.S. federal securities laws and encouraging consultation with the SEC in connection with the legal analysis of such offerings (*see* Jones Day Commentary, "SEC's Investigative Report Raises Difficult Questions for ICO Issuers").
- The Federal Trade Commission, the U.S. antitrust and consumer protection regulator, announced the creation of its FTC Blockchain Working Group on March 16, 2018. The working group is designed to build on the FTC's expertise in blockchain technology and will facilitate coordination of enforcement actions. To that end, use of blockchain technology raises potential issues under Sherman Act § 1 (no collusion), Sherman Act § 2 (no monopolization), Federal Trade Commission Act § 5 (no unfair competition), and Clayton Act § 7 (no anticompetitive mergers) (*see* Jones Day Commentary, "Blockchains and Antitrust: New Technology, Same Old Risks?").
- In July 2017, the Uniform Law Commission approved a Uniform Regulation of Virtual Currency Business Act. The regulation seeks to harmonize state laws by setting out which virtual currency activities should be considered as money transmission and require licensing, and includes provisions around reciprocity, consumer protection, cybersecurity, anti-money laundering, and licensee supervision. It remains to be seen which states will adopt the model law and how much harmonization at the state level will occur as a result.

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United States of America *continued*

CASE LAW	*SEC v. REcoin Group Foundation, LLC et. al.*: On September 29, 2017, the SEC charged the promoters of the REcoin and Diamond Reserve Club ICOs with defrauding investors, marking the first time the SEC has brought an enforcement action related to ICOs. In a civil suit filed in the U.S. District Court for the Eastern District of New York, the SEC alleged that the defendants illegally offered unregistered securities and made fraudulent misstatements that were designed to deceive investors in connection with the ICOs. In a parallel criminal fraud case filed in the Eastern District of New York, the defendants challenged the SEC's authority to regulate cryptocurrencies and ICOs. On September 11, 2018, the court ruled as part of a motion to dismiss that a reasonable jury could find that the cryptocurrencies in question were "securities" for federal securities law purposes. *CFTC v. CabbageTech, Corp. et. al.*: On March 6, 2018, the Eastern District of New York entered a preliminary injunction against CabbageTech, Corp. d/b/a Coin Drop Markets, stating that cryptocurrencies can be regulated by the CFTC as commodities. The court's decision stems from the CFTC's January 18, 2018, complaint charging the defendants with fraud and misappropriation in connection with purchases and trading of the virtual currencies Bitcoin and Litecoin. On August 24, 2018, the court entered final judgment ordering Coin Drop Markets to pay more than $1.1 million in civil monetary penalties and restitution. *Alibaba Group Holdings Ltd. v. Alibabacoin Foundation*: On October 22, 2018, the U.S. District Court for the Southern District of New York issued a preliminary injunction in a case involving a trademark dispute between Alibaba Group Holdings Ltd., the multinational web-services conglomerate, and cryptocurrency issuers that had allegedly used Alibaba trademarks to promote their coin offering. At issue was whether Alibaba sufficiently established personal jurisdiction over the defendants, which were Dubai and Belarus companies. Part of that consideration involved a discussion of the applicability of New York's long-arm statute, which authorizes the state's courts to "exercise personal jurisdiction over any non-domiciliary" that "transacts any business within the state." The defendants contended that no transactions occurred in the United States because the ledger entries were made in Belarus and the defendants are located abroad. The court found this argument unpersuasive after Alibaba produced a list of email addresses involved in the coin transactions, which revealed that at least one purchaser was a New York resident. Accordingly, the court deemed that the defendants' activities constituted purposeful transaction of business within New York and New York's long-arm statute applied.
KEY LEGAL ISSUES	The key U.S. legal considerations will be the interaction and potential harmonization of disparate federal and statewide legal and regulatory frameworks. In addition, U.S. regulators have reiterated the full applicability of current regulations to applications of blockchain technologies, notwithstanding the fact that these regulations were enacted for a previous technological era and to address entirely different operational paradigms.

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United States of America *continued*

USEFUL PUBLICATIONS	SEC—"Report of Investigation Pursuant to Section 21(a) of the Securities Exchange Act of 1934: The DAO":
	"SEC Issues Investigative Report Concluding DAO Tokens, a Digital Asset, Were Securities"
	"Investor Bulletin: Initial Coin Offerings"
	OCC—"Exploring Special Purpose National Bank Charters for Fintech" and related releases:
	"Comptroller's Licensing Manual Draft Supplement: Considering Charter Applications From Financial Technology Companies"
	"Policy Statement on Financial Technology Companies' Eligibility to Apply for National Bank Charters"
	FINRA—"Distributed Ledger Technology: Implications of Blockchain for the Securities Industry"
	"What is Blockchain, and Why Should I Care?"
	"Regulatory Notice 18-20: Digital Assets"
	"Special Notice: Financial Technology Innovation"
	CFTC—"Order of Registration: In the Matter of the Application of LedgerX LLC for Registration as a Swap Execution Facility"
	"CFTC Staff Advisory No. 18-14 Advisory with respect to Virtual Currency Derivative Product Listings"

UNITED KINGDOM

OVERVIEW

The United Kingdom (and English law) is generally recognized as being a transparent, predictable, and business-friendly jurisdiction for blockchain technologies, in particular giving effect to commercial parties' freedom to contract on terms that they consider appropriate.

The common law approach to formation of contracts also gives a good level of flexibility to parties to enter into binding contracts using new technologies, without the need for further legislation or regulation.

Both the UK government and the Financial Conduct Authority ("FCA") have been early adopters of digital strategies and are focused on encouraging innovation, including in relation to blockchain technologies. As a result, there is a thriving fintech sector that has grown up in the United Kingdom in recent years.

At the same time, the United Kingdom is a highly regulated market—particularly for financial services—and any use of blockchain technologies will have to navigate the United Kingdom's overarching legal requirements in areas such as data protection and consumer law as well as meeting general requirements for large companies and regulated entities to have adequate systems and processes to manage risk in their businesses.

LEGISLATION/ REGULATION

There is no specific legislation or regulation that has been passed in the United Kingdom for blockchain technologies, and none is expected imminently—largely due to the existing flexible, common law nature of English law that already can accommodate contracts conducted on the blockchain.

The United Kingdom's financial regulator, the FCA, has run several initiatives involving blockchain technology, notably the introduction in May 2015 of a "regulatory sandbox" open to both regulated and unregulated firms to trial new technologies for financial services in a customized regulatory environment. As of July 2018, the FCA announced that it was adding 29 organizations to its fourth cohort of firms accepted into the UK regulatory sandbox. Over 40 percent of companies accepted to cohort four are using DLT. Of these, six are using DLT to automate the issuance of debt or equity. Two are using DLT to support the provision of insurance.

The FCA published a discussion paper in April 2017 seeking views on the future development of blockchain technologies in regulated financial markets, noting that the FCA generally takes a "technology neutral" approach to regulating financial services and are interested in considering whether there is anything distinctive about blockchains that would require a different approach. In December 2017, the FCA provided an overview on the feedback received in response to the discussion paper, with such feedback suggesting that the FCA's current rules are flexible enough to accommodate applications of various technologies, including the use of blockchain by regulated firms.

The FCA also published a consumer warning regarding the risks of ICOs under which the FCA stated that "ICOs are very high-risk, speculative investments" and that evaluations regarding FCA regulation of ICOs are determined on a case-by-case basis.

On September 13, 2017, it was announced that the FCA, in collaboration with consortium R3, Royal Bank of Scotland, and a third unnamed bank, was developing a blockchain technology-based application for the mortgage industry to improve the supervision.

On August 7, 2018, the FCA announced, in collaboration with 11 other financial regulators, the creation of the Global Financial Innovation Network, which seeks to provide a more efficient way for innovative firms to interact with regulators, helping them navigate between countries as they look to scale new ideas. It will also create a new framework for cooperation between financial services regulators on innovation-related topics, sharing different experiences and approaches.

The UK government has published several papers on the use of blockchain technologies to supply public and government services and has trialed disbursement of student loans and welfare payments using the new technology. It is currently in the second phase of a major project to assess how blockchain technology and smart contract could revolutionize land registration and land transfers in the United Kingdom.

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United Kingdom *continued*

CASE LAW	No significant reported cases on blockchain technology. Various UK tax cases have acknowledged the findings in the *Hedqvist* case that exchange of a unit of virtual currency (such as a bitcoin) to a fiat currency is exempt from VAT as analogous to an FX transaction.
KEY LEGAL ISSUES	The general position under English law is that it should be possible to enter into binding agreements and execute those agreements via a blockchain as long as the usual requirements for a valid contract under English law are met—offer, acceptance, intention to create legal relations, certainty of terms, and passing of consideration. English law and English courts also have a long history of accepting electronic and digital evidence as proof of ownership of tangible assets, so there are good arguments that physical assets that are tokenized and traded via a blockchain system can be upheld and enforced using the existing legal framework and historic case precedent. In relation to the key issue of whether an asset that exists only as a block of data in a blockchain would be recognized in English law as property, there are conflicting academic views and authorities (none of them in the context of blockchain assets). There is clear English law authority that information stored on a database is not property that is capable of possession and therefore can be subject to security or attachment. However, there also have been cases where assets that exist only electronically, such as carbon credits, have been judged to be "property" at common law, consistent with a long history of English case law that recognizes interests in intangible assets (the "chose in action"). While ultimately the English courts will have to address this specific issue, it seems more likely that the latter view will ultimately prevail, supporting the creation of transferrable assets via blockchain technology under English law. If so, English law has a wide range of common law and equitable remedies that can be used to assert title and recover assets in a disputed situation, including proprietary restitutionary claims and claims for unjust enrichment. To the extent that blockchain systems are used to deal in or with managed regulated products, particularly financial products, the United Kingdom's principles-based regulatory systems are expected to continue to apply to such products, consistent with statements made by the FCA in the context of ICOs. The mere fact that a transaction in a regulated product takes place via a blockchain will not relieve parties from complying with their existing regulatory obligations.
USEFUL PUBLICATIONS	UK Government—"Distributed Ledger technology: beyond blockchain" "UK Digital Strategy 2017" FCA—"Discussion paper on Distributed Ledger Technology" "Feedback Statement on Discussion Paper 17/03" "Consumer Warning about the Risks of Initial Coin Offerings"

FRANCE

OVERVIEW

The focus within France on blockchain technologies has, so far, been within the financial sector. In particular, the French financial supervisory authorities have historically been very proactive regarding any evolution in the financial industry that would require adjustments in rules and regulations. Their approach is normally through regular consultation papers prior to the issue of any substantial new piece of legislation or guidelines and recommendations to clarify how practically to comply with certain rules.

France has a long history of early implementation of technology within the financial sector, notably in having dematerialized all the holding of securities since 1984 and having computerized all this part of the back-office business, followed with electronic trading and settlement in the late 1980s.

This culture has spread more recently into the fintech world, with specific legislation tailored to crowd funding and new payment solutions. However, the *Banque de France* has shared its concerns with respect to cryptocurrency (such as bitcoin), the anonymity surrounding its use, and the risk of value fluctuating in a very unpredictable way.

LEGISLATION/ REGULATION

France has adopted two pieces of legislation that explicitly refer to blockchain technology.

- An Ordinance dated April 28, 2016, set out the possibility for certain classes of commercial paper to be held and transferred via a blockchain, the characteristics of which will be detailed in an implementing decree (to be issued before the end of the year); *see* art. L. 233-12 of the Monetary and financial code.
- Law n°2016-1691 of December 9, 2016 (art. 120) authorized the French government to determine, by an ordinance, the rules that could allow for the holding and transfer of nonlisted securities via a blockchain system. On that basis, the French Treasury *launched a consultation process* at the end of March 2017 to identify the laws and regulations that should be taken to enable such new digital securities to be held and transferred.

A bill (Loi PACTE) is being examined before the Parliament and is expected to be passed in Q1 2019 at the latest. The bill proposes to introduce two regulatory regimes governing activities relating to digital assets:

- The first aims to provide an optional approval for any initial coin offering in France granted by the French market authority to the extent that such offering is accompanied with documentation providing investors with certain pieces of information relating to digital assets.
- The second aims to provide a regulatory framework for entities proposing to offer services relating to digital assets (e.g., safekeeping, trading, advising, placing). Such entities may apply for a specific license, provided they comply with organizational and good-conduct rules.

CASE LAW

There is no particular case law that has involved any legal issue resulting from the use or implementation of blockchain technology.

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France *continued*

KEY LEGAL ISSUES	Legal issues arising from the use of blockchain technologies depend on its use and purpose, and whether it is confined to a contractual purpose (such as smart contracts) or if it interacts with regulatory issues. Smart contracts per se should not raise substantial legal issues since it is left to the parties to a contract to have the performance of their obligation be automatic (with no individual interference), as soon as the basics of creation and perfection of the contract are complied with. In respect of the use of distributed ledger technology ("DLT") in banking or financial business, issues may vary depending on whether its purpose is to implement a new way of storage of information (therefore with no particular regulatory impact), or whether the information contained in the DLT has a more substantial value (i.e., representing rights itself). France is used to handling dematerialized assets, and therefore the conceptual gap with DLT applied to securities, transfer of assets, etc., will be managed. The challenges are rather on the regulatory side, and the extent to which confidence may be built with the regulators on this rather complex technology based on trustless principles. It should be noted that projects implementing blockchain technologies may raise significant concerns with respect to the French and, more generally, EU data protection framework, if the records processed by the blockchain involve personal data (i.e., relate to an individual who can be identified directly or indirectly). Potential data protection risks involved in blockchain projects should be carefully assessed and mitigated.
USEFUL PUBLICATIONS	Treasury consultation of March 24, 2017, about the use of blockchain technology for nonlisted securities Presentation from the AMF in May 2017 on Blockchain and Regulation Publication from the AMF in February 2018 of the results of the consultation on ICOs and potential regulation Publication from the French data protection authority ("CNIL") including their preliminary analysis on the compatibility of blockchain technologies with the current data protection framework

GERMANY

OVERVIEW	Germany is very supportive of DLT and blockchain-based technology. In early 2017, the German government established a FinTech Advisory Committee (*FinTechRat*) to promote fintech technology. The advisory committee consists of 20 members from banks and insurance companies, professors, and government representatives. In Germany there is no specific DLT or blockchain-related legal framework. German law is generally agnostic as to the use of technology. Accordingly, there are no express restrictions on the use of DLT or blockchain. General principles of German law, such as contract law, apply. The German Financial Supervisory Authority (*Bundesanstalt für Finanzdienstleistungsaufsicht* or "BaFin") has set up a special task force cooperating with the industry to discuss and develop DLT-based technologies, in particular in the finance sector. For example, the German central bank, *Deutsche Bundesbank*, in cooperation with *Deutsche Börse*, developed a functional prototype for the blockchain-based settlement of securities.
LEGISLATION/REGULATION	Germany does not have any special DLT or blockchain legislation. German law is generally agnostic as to the technology. Accordingly, there are no express restrictions on the use of DLT. Since its coming into force in 1900, the German Civil Code has embraced the technological revolution over the past 100-plus years without the need for substantial change (save for the addition of European law-driven consumer protection provisions), and therefore it is already proven to be flexible enough to provide a legal framework for blockchain-based products. From a regulatory perspective, there are no special rules relating to DLT or blockchain. BaFin takes the view that at the moment, DLT and blockchain technology does not require special treatment but are to be considered within the existing regulatory framework.
CASE LAW	In 2012, the German Federal Supreme Court held that, with regard to an air flight booking system, information entered into an electronic system needs to comply with general principles of contract. In that case, the entry of the phrase "unnamed" instead of the name of the flight passenger was considered not to be in line with certainty of contract and did not constitute a valid identification of a party to the flight contract, even though the system issued a corresponding flight ticket. On September 25, 2018, the Higher Regional Court of Berlin ruled that bitcoin does not qualify as a "financial instrument" for purposes of the German Banking Act. The defendant in the case allegedly ran an unlicensed bitcoin trading platform. On appeal, the Higher Regional Court of Berlin ruled the defendant's activity was not regulated activity under the German Banking Act because bitcoin does not represent "units of account," given that it lacks a stable value and is not an accepted means of payment. The holding runs contrary to the opinion of BaFIN, which is described in more detail below. Following the case, BaFIN stated that it considers the holding limited to the facts of the case and will not change its stance in light of the holding.

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Germany *continued*

KEY LEGAL ISSUES	The key legal issues to consider depend on the function and role that DLT and blockchain play in a transaction. Even though DLT-based systems may operate as a "virtual reality," they remain connected to the real world. These real-world connections and the specific function or role that DLT plays for a certain transaction will govern the application of German law concepts like offer and acceptance, mistake, fraud, recession, damages for breach of contract, and the principle of good faith and *bonos mores* to blockchain-based transactions. It should therefore be possible to enter into contracts based on DLT or blockchain-based technology as long as offer and acceptance can be established. As with most other technologies the parties may wish to provide for greater legal certainty by agreeing on certain terms of use for a blockchain-based system. These terms of use could provide certainty as to the key legal issues in connection with blockchain, i.e., the law applicable to the system that (typically) operates across borders, the identification of the relevant parties to a transaction, liability between the parties, consequences of a mistake and means of rectification in particular in relation to smart contracts. Blockchain may also be used as a means for executing a traditional contract, e.g., whereby the parties agree that certain parts of the contract are executed on a blockchain. There are also some German law particularities, most notably with regard to the creation and transfer of assets, which should be borne in mind when thinking of creating or transferring assets on blockchain. While it may be relatively simple to transfer a claim on blockchain, this may be more difficult with regard to other types of assets. For example, under German law, the creation of securities requires a written signature of the issuer of the issued securities. It may therefore be difficult to create a blockchain-based security without any signed document, but it should be possible to arrange for a blockchain-based transfer of these securities after they have been validly created. Similarly, the transfer of certain assets, such as shares or real estate, is subject to form requirements, e.g., a notarization or a registration in a register (such as the land registry), which cannot be mirrored on the blockchain. From a regulatory point of view, it should be noted that certain activities relating to financial instruments constitute regulated activities. The definition of "financial instruments" is very broad and includes not only, for example, securities and derivatives but also "units of account" that operate similar to a currency but are not an official currency. The BaFin takes the view that bitcoins qualify as "units of account" (for exchange into money) and therefore as a financial instrument for regulatory purposes. As a consequence, while the use and the mining of bitcoins does not constitute a regulated activity, certain other activities, such as trading or market making in bitcoins may fall within the scope of a regulated activity. Therefore, when operating a DLT or blockchain-based system, the regulatory implications should be borne in mind. In addition to financial instruments, DLT or blockchain-based systems may also fall within the category of e-money or the provision of payment services, which may result in license requirements depending on the type of service provided.
USEFUL PUBLICATIONS	*Deutsche Bundesbank* and *Deutsche Börse* developed a functional prototype for the blockchain-based settlement of securities BaFin—"Bitcoins: Supervisory assessment and risks to users" (English version) BaFin—"Blockchain-technology" (German version) BaFin—"Distributed Leger: The technology behind virtual currencies using blockchain as an example" (German version)

ITALY

OVERVIEW

In Italy, investments in blockchain technology by traditional operators are still limited; however, banks and financial intermediaries are expressing a strong interest in such technology. A recent survey carried out by the Bank of Italy has revealed that many of the banks classified as significant by the Supervisory Authority are launching fintech projects. The Italian Bank Association ("*Associazione Bancaria Italiana*" or "ABI"), along with a pilot group of Italian banks, has started an operative test [*sperimetazione operativa*] for implementing blockchain technology systems, which has successfully passed the initial phase of testing their blockchain-powered interbank system.

The Bank of Italy has taken on a proactive role in international and EU committees and bodies in order to harmonize a common framework of rules and supervisory practices. These will support the development of fintech and enable the establishment and evolution of a fintech ecosystem.

To that end, the Bank of Italy launched a fintech hub on its website, which represents "an attempt to adopt a business-friendly approach towards those who are interested in establishing a start-up, opening a new line of activity, etc." Through this hub, the Bank of Italy can gather information on any new matter that might be useful for providing rules aimed at reducing regulatory uncertainty, which is one of the main deterrents for new businesses.

Furthermore, a new task force on financial innovation has been created within the General Directorate for Banking and Financial Supervision for the purposes of: (i) better understanding trends and initiatives from the supervisor's perspective; (ii) promptly detecting market changes in order to analyze their effects and risks; and (iii) promoting the harmonization of supervisory practices, providing, whenever possible, suitable rules.

Italy has recently joined the Blockchain Partnership.

LEGISLATION/ REGULATION

Italy does not have any DLT or blockchain-specific legislation or regulatory provisions concerning DLT.

Nevertheless, in July 2017, Legislative Decree No. 231/2007 (providing for anti-money laundering rules) was amended by Legislative Decree No. 90/2017, which implemented the IV AML directive. On that occasion, the Italian legislature broadened the scope of Italian AML legislation by, inter alia, providing that entities exchanging virtual currencies must comply with the Italian AML requirements. Notwithstanding the foregoing, this provision still needs to be implemented by executive regulations.

CASE LAW

There is no particular case law that has involved any legal issue resulting from the use or implementation of blockchain technology. However, some of the main resolutions issued with regard to virtual currency include:

- Judgment of *Tribunale di Verona* of January 24, 2017;
- Antitrust Authority (*Autorità Garante della Concorrenza e del Mercato*) resolution on tokens*;*
- *Commissione Nazionale per le Società e la Borsa* ("Consob") resolutions on offering of virtual currency via websites;
- *Risoluzione* no. 72/E of 2016 issued by the Italian Tax Authority (*Agenzia delle Entrate*); and
- Ruling submitted to the Italian Tax Authority (*Agenzia delle Entrate*) on January 22, 2018.

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Italy *continued*

KEY LEGAL ISSUES	Legal issues related to blockchain or DLT mainly arise from how they are used. In particular, issues may arise from the use of blockchain or DLT systems for contractual purposes (e.g., smart contracts) or from potential interactions between blockchain or DLT and regulatory requirements. Moreover, there are some Italian laws, like those dealing with the transfer of assets, that should be taken into consideration when thinking of creating or transferring assets via smart contracts. For example, under Italian law, real estate assets may be transferred only if specific formalities are fulfilled (i.e., notarization and registration in registers such as the "*conservatoria dei registri immobilari*"). Such formalities cannot be mirrored on the blockchain. Some issues may arise from a regulatory prospective with regard to virtual currencies. Virtual currencies, per se, are not deemed "financial instruments." Therefore, the mining and use of virtual currencies, in principle, do not fall within the scope of any regulated activity. Nevertheless, specific and more complex financial activities, such as margin trading involving virtual currency, are deemed regulated activities reserved only to authorized intermediaries. On January 30, 2015, the Bank of Italy issued a report providing for general principles regarding the use of "virtual currencies." The Bank of Italy has advised, inter alia, that certain uses of virtual currencies might be in breach of Italian regulations involving investment activities reserved to authorized entities. Such breaches are punishable in accordance with Art. 166 of Legislative Decree No. 58/98. Moreover, the Bank of Italy issued a new alert on March 2018. Consob has qualified "particular" offerings of virtual currency through websites as public offerings of financial products ("*offerta al pubblico di prodotti finanziari*") according to article 1, paragraph 1, letter (t) of Legislative Decree No. 58/1998. Pursuant to Article 94 of Legislative Decree No. 58/98, financial products may be offered to the public only if a prospectus is published in advance, unless the offer meets certain exemption requirements.
USEFUL PUBLICATIONS	ABI web site for press releases Consob website (English version) Bank of Italy web site "Canale fintech" and the page reserved for fintech updates.

SPAIN

OVERVIEW	Spain is committed to encouraging innovation in the field of DLT and blockchain technology. Companies from different sectors are increasingly attracted by the substantial agility and transparency advantages this technology can offer. Most of the major Spanish companies have formed the consortium Alastria, which is the first semi-public blockchain infrastructure in Spain. The financial sector is particularly focused on the development of this technology. Banks are experimenting with pilot transactions, including payment transfers, lending, trade finance and capital markets. In this regard, the so-called "Fast Track Listing" project has been developed by the National Securities Market Commission ("CNMV"), the Spanish Stock Exchanges and Markets (*Bolsas y Mercados Españoles*), and several financial institutions. The growing interest in this technology stands in contrast to the absence of DLT or blockchain-specific regulation. However, existing rules and the general principles of Spanish law, such as civil and commercial laws, capital markets legislation, consumers' protection, prevention of money laundering, etc., may be applicable, depending on how DLT or blockchain technology is being leveraged. The Bank of Spain and the CNMV released a joint statement regarding cryptocurrencies and initial coin offerings, which warns parties of the risks involved (e.g., price volatility and significant risk of loss of invested capital) and encourages issuers to comply with capital markets legislation.
CASE LAW	There is no particular case law that has implicated any legal issue resulting from the use or implementation of blockchain technology.
KEY LEGAL ISSUES	The main advantages of this technology are focused on improving the traditional system of purchasing and transferring securities and rights. However, the implementation of the technology may be challenged by the existing legal system and the uncertainties generated by new technology. It should therefore be possible to enter into contracts based on DLT or blockchain-based technology as long as the existing legal requirements are met (e.g., consent, offer and acceptance, object and cause). As with most other technologies, the parties may wish to provide for greater legal certainty by agreeing on certain terms for a blockchain-based system and smart contracts. These terms could provide certainty as to key legal issues, such as: the applicable law in cross-border transactions, the identification of the relevant parties to a transaction, the free and valid consent rendered by the parties, the nature of obligations subject of this type of contracts, the liability between the parties, the consequences of a mistake in the provisions of the contract or the consequences of any ineffectiveness that invalidates the contract, etc. Today, there are a large number of operative or non-deterministic provisions that, either by their very nature or by the formalities, cannot be self-executed with this technology. From a regulatory point of view, it should be noted that certain activities relating to financial instruments constitute regulated activities. The definition of "financial instruments" is very broad, and although cryptocurrencies and tokenized assets are not expressly included in such definition, these digital assets may contain features very similar to financial instruments, depending on how their embedded rights are structured/described. Therefore, the CNMV may consider them as a financial instrument for regulatory purposes in order to protect investors. In addition to financial instruments, cryptocurrencies may also fall within the category of e-money or the provision of payment services, which may result in license requirements depending on the type of service provided.
USEFUL PUBLICATIONS	Act 5/2015, of April 27, 2015, on promotion of corporate funding Joint press statement by CNMV and Banco de España on "cryptocurrencies" and "initial coin offerings," dated February 8, 2018. CNMV considerations on cryptocurrencies and ICOs addressed to market professionals, dated February 8, 2018.

THE NETHERLANDS

OVERVIEW

The discussion on the use of blockchain technology is very active in the Netherlands. Interest in and awareness of DLT, which has the potential to become the most important means of exchanging data in a secure and efficient manner, is high both in public and private sectors. Several organizations have been set up to coordinate efforts in this field, most notably the Dutch Blockchain Coalition. Alliances like these are a great example of collaboration between industry, government, and knowledge institutions in the Netherlands (and abroad).

In the Netherlands, blockchain is no longer just a thing of the future: the technology is used to set up innovative new applications and to improve existing processes. Dutch financial institutions, as well as the land registry and the Dutch civil law notaries, are experimenting with blockchain-based solutions. In addition, there is a thriving start-up ecosystem stimulated by the presence of top tier universities.

While on a national level no blockchain-specific legislation has been adopted, the existing legal framework allows for the use of blockchain technology, and the Dutch courts have repeatedly shown that they are willing to adapt and move with the times.

LEGISLATION/ REGULATION

The Netherlands has not adopted any legislation that specifically refers to blockchain technology. Several workgroups have been established to review the need for regulation. Even so, in most cases the existing legal framework allows for the use of blockchain technology or can be applied to blockchain use cases. For instance, Dutch law allows for contracts to be concluded electronically if certain conditions are fulfilled. A smart contract may therefore under certain circumstances qualify as a contract under Dutch law. Conducting a thorough review of each specific application and the potentially applicable rules and regulations is essential.

The Dutch Authority for the Financial Markets ("AFM") and the Dutch Central Bank ("DCB") have issued public statements confirming that cryptocurrencies currently are not supervised, although the AFM noted that depending on the character of the token, ICOs may fall under the Financial Supervision Act (i.e., should be treated as securities).

As a European Union Member State, the Netherlands is subject to EU law. Rules and regulations such as the fifth Anti-Money Laundering Directive—which will apply to cryptocurrency platforms and wallet providers—and the General Data Protection Regulation ("GDPR") may therefore be relevant.

CASE LAW

There are several cases in which the Dutch courts dealt with blockchain technology. These cases all revolve around the cryptocurrency bitcoin. In adjudicating these cases, the Dutch courts have repeatedly shown that they are willing to adapt and move with the times. The courts have, among others, determined that:

- Bitcoin does not qualify as "money" in the legal sense;
- Failure to comply with an obligation to "pay" bitcoin can be grounds to open a bankruptcy proceeding;
- A Dutch bank was allowed to terminate its banking contract with a company that buys and sells bitcoin for clients, as the company refused to comply with the bank's requests regarding the identity of the clients and providing assurances that the company or its clients were not engaged in money laundering.

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The Netherlands *continued*

KEY LEGAL ISSUES	Key legal issues depend on the area of use: • **Blockchain technology in general**: Key matters include: (i) the effects of dissolution and rescission of contracts, and of bankruptcy, which have retroactive effect or require obligations that have already been performed to be unwound; and (ii) how to apply GDPR to personal data stored in the blockchain. • **Smart contracts**: Key matters under discussion include whether the smart contracts represent legal acts and qualify as legally binding contracts, and how to deal with the immutability aspects of the smart contract. • **ICOs**: Whether the tokens qualify as securities (and hence whether an ICO may qualify as offering securities to the public, triggering prospectus requirements). • **Asset ownership registrations on blockchain**: Liability, insolvency risks, property law (can a transfer of ownership on a blockchain qualify as a legal transfer?). • **Cryptocurrencies**: The DCB has concluded that (most) cryptocurrencies cannot be considered "money" (legal tender); access to cryptocurrency wallets by, for example, a trustee in bankruptcy.
USEFUL PUBLICATIONS	• The Dutch Blockchain Coalition's report on smart contracts • The AFM and DCB have established an Innovation Hub to support and provide informal advice to market participants

PEOPLE'S REPUBLIC OF CHINA

OVERVIEW	Chinese investors and consumers have shown intense interest in all forms of electronic payment systems. It is estimated that in 2016, Chinese consumers made 50 times more mobile payments than did U.S. consumers, for a total volume of US$5.5 trillion. As for blockchain transactions, China hosts the largest bitcoin exchange in the world (BTC China), and China is the third-largest bitcoin market. Chinese authorities have taken a cautious approach toward blockchain transactions. Bank officials do not recognize blockchain payment methods as currencies, but they do recognize their utility as personal assets. Bank officials have indicated the likelihood of regulatory restrictions on blockchain transactions while also researching and discussing a state-banked blockchain currency.
LEGISLATION/ REGULATION	Chinese authorities were initially skeptical of blockchain-based payment methods. In December 2013, the People's Bank of China ("PBOC," China's central bank, banking regulatory authority, and monetary policy institution) passed a series of regulations preventing Chinese banks from accepting and using bitcoin as a currency. The PBOC's directive indicated that these restrictions were needed to "protect the status of the renminbi as the statutory currency, prevent risks of money laundering, and protect financial stability." The PBOC further indicated that bitcoin should not "be circulated or used in the marketplace as a currency." Since that time, Chinese bank officials have shown some ambivalence. On one hand, they have been supportive of the use and exchange of blockchain payment units by and between private individuals (while still not allowing these methods to function as currencies). In June 2017, for example, a PBOC official said in an interview that "Bitcoin does not have the fundamental attributes needed to be a currency as it is a string of code generated by complex algorithms[,] but I do not deny that virtual currencies have technical value and are a type of asset." On the other hand, bank officials have expressed strong concerns about unrestricted blockchain trading. In February 2017, PBOC indicated that it would shut bitcoin exchanges that did not comply with money laundering, foreign exchange management, and payment and settlement rules, causing these exchanges to self-impose a moratorium on bitcoin withdrawals.
KEY LEGAL ISSUES	In September 2017, the PBOC announced a complete ban on ICOs, declaring them illegal and requiring all ICOs to cease immediately. A joint statement from the Chinese authorities and the PBOC indicted that individuals and organizations involved in ICOs must refund investors for any amounts raised to date. The move is aimed at protecting investors and "dealing with the risks properly," according to the PBOC's statement. At the same time, all virtual currency trading platforms based in Beijing and Shanghai were required to cease operations. The PBOC has, however, previously announced plans to release its own blockchain-based currency. PBOC released a research paper in 2017 in which it predicted a digital currency that would allow consumers to carry out direct and paperless transfers to merchants as well as other individuals, so further developments remain possible.

HONG KONG (SAR)

OVERVIEW

The use of blockchain and DLT in Hong Kong may be described as being in its infancy. The Hong Kong government has recognized the potential value of blockchain and has encouraged relevant organizations to explore its use.

LEGISLATION/ REGULATION

There is no specific legislation relating to DLT, and none is expected in the near future.

In November 2016, the Hong Kong Applied Science and Technology Research Institute ("ASTRI") published a white paper on DLT and three areas where proof-of-concept for DLT applications should be carried out: mortgage loans, trade finance, and digital identity management. A second white paper will be published in the second half of 2017, which will cover the regulatory implications of DLT and in the banking and payment industry. Depending on the contents of this second white paper, it may form a springboard from which more concrete initiatives will be adopted by the Hong Kong government.

Separately, the Financial Services Development Council (established by the Hong Kong government in 2013 in response to the financial services industry's call for a high-level government advisory body to support the sustained development of the industry) also published a white paper in May 2017 that examined how Hong Kong can develop its blockchain capabilities to serve the region.

The Hong Kong Monetary Authority ("HKMA") announced the establishment of a regulatory sandbox on September 6, 2017, to facilitate the pilot trials of mobile payment services and blockchain business initiatives of authorized institutions before they are launched on a fuller scale.

Additionally, on July 17, 2018, the HKMA announced that it would jointly launch a trade finance platform in September using Blockchain technology. The effort will involve 21 banks, including HSBC Holdings plc and Standard Chartered plc.

On September 29, 2017, the Securities and Futures Commission ("SFC") established the "Fintech Contact Point" to enhance communication with businesses involved in the development and application of financial technology that intend to conduct regulated activities in Hong Kong. Under the Securities and Futures Ordinance ("SFO"), no person may carry on a business in a regulated activity without a license granted by the SFC. Parties are urged to contact the Fintech Contact Point if they intend to engage in regulated activities like delivering financial services through DLT on a "Fintech enquiry form."

Simultaneously, the SFC announced the formation of a Fintech Advisory Group tasked with obtaining information on the latest trends of fintech; collecting stakeholders' input; identifying the opportunities, risks, and regulatory perimeter implications of fintech; and broadening the understanding of fintech as an evolution of the financial services industry.

In addition, the SFC announced a regulatory sandbox initiative to provide a confined regulatory environment for qualified firms to operate regulated activities before Fintech is used on a fuller scale. The Sandbox would enable qualified firms, through close dialogue with and supervision by the SFC, to readily identify and address any risks or concerns relevant to their regulated activities.

On September 5, 2017, the SFC issued a statement regarding ICOs and the applicability of existing securities regulations, which expressed a facts-and-circumstances approach to whether digital tokens issued by ICOs are "securities" as defined in the Securities and Futures Ordinance.

On December 11, 2017, the SFC issued a reminder of the risks associated with the provision of financial services in relation to bitcoin futures contracts. Relevant business activities, including the relaying or routing of bitcoin futures orders and providing advisory services in relation to bitcoin futures, could be prohibited without the requisite Type 2 (dealing in futures contracts) or Type 5 (advising on futures contracts) licenses or other relevant licenses.

On February 9, 2018, the SFC issued another alert to investors regarding the potential risks of dealing with cryptocurrency exchanges and investing in ICOs. The SFC has sent warnings to seven cryptocurrency exchanges in Hong Kong, advising them that certain cryptocurrencies may be "securities," as defined in the Securities and Futures Ordinance, and therefore require a license to trade.

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Hong Kong (SAR) *continued*

LEGISLATION/ REGULATION	On March 19, 2018, the SFC disclosed that it had taken regulatory action against Black Cell Technology Limited, which had conducted unauthorized promotional activities and unlicensed regulated activities by advertising the uses of its digital token (known as "KROPS") on its website generally accessible by members of the Hong Kong public. Following the SFC's regulatory action, Black Cell agreed to: (i) halt the sale of KROPS and to unwind all of its transactions with Hong Kong customers; and (ii) place the following pop-up message on its website: "The following token sale is not open for American citizens (and/or U.S. residents), Hong Kong citizens and any citizen or resident of a country that does not allow participation." On October 15, 2018, outgoing SFC chairman Carlson Tong Ka-shing stated that the SFC is exploring ways to regulate cryptocurrency trading platforms operating in Hong Kong in a manner that is consistent with licensed trading platforms. Moreover, Tong stated that a complete ban on trading platforms is not the right approach in today's world, as transactions are still being conducted via overseas platforms.
CASE LAW	There are no reported or current cases relating to DLT.
KEY LEGAL ISSUES	In Hong Kong, whether the use of DLT complies with current regulatory requirements is an area that remains unexplored or has received little in-depth investigation. To date, regulatory authorities in Hong Kong have issued little by way of regulatory guidance or control principles. It is unclear whether existing laws can adequately deal with the regulatory and legal issues associated with the decentralized and cross-border nature of DLT platforms. This issue could be highlighted by an increase in cross-border bitcoin activity following China's September 15, 2017, request for bitcoin exchanges and trading platforms to shut down. Currently, ASTRI is planning to engage legal experts to take part in a further study to develop sound regulatory guidance and control principles.
USEFUL PUBLICATIONS	ASTRI—"Whitepaper on Distributed Ledger Technology" FSDC—"Hong Kong—Building Trust Using Distributed Ledger Technology" Steering Group—"Report of the Steering Group on Financial Technologies" SFC—"Fintech enquiry form" SFC—"Circular to announce the SFC Regulatory Sandbox" SFC—"Statement on initial coin offerings" SFC—"Circular to Licensed Corporations and Registered Institutions on Bitcoin futures contracts and virtual currency-related investment products" SFC—"SFC warns of virtual currency risks" SFC—"SFC's regulatory action halts ICO to Hong Kong public" HKMA—"Guidelines and Circular: Fintech Supervisory Sandbox (FSS)"

SINGAPORE

OVERVIEW

The legal system in Singapore is derived, in large part, from the English common law system and as a result bears a great deal of similarity to the English legal system, particularly in relation to contract and commercial law.

Singapore, similar to the United Kingdom, is generally recognized as being a transparent, predictable, and business-friendly jurisdiction for blockchain technologies, in particular giving effect to commercial parties' freedom to contract on terms that they consider appropriate.

A study undertaken by the Lucerne University of Applied Sciences and Arts, comparing various cities across the world on the basis of their respective political and legal, economic, social, and technological environments, identified Singapore as the city most suitably placed to develop into a fintech hub.

While the sheer number of start-ups engaging in the blockchain technology industry in other parts of Asia (such as Japan and South Korea) may be substantially larger than Singapore, the government in Singapore appears to be acutely aware, and is taking a number of proactive measures to ensure, that Singapore is considered to be a favorable jurisdiction for the development of the fintech industry.

The common law approach, adopted in Singapore, to the formation of contracts also gives a good level of flexibility to parties to enter into binding contracts using new technologies, without the need for further legislation or regulation. Similar to the United Kingdom, Singapore is also a regulated market for financial services—and any use of blockchain technologies will have to comply with Singapore's laws relating to data protection and consumer law.

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Singapore *continued*

LEGISLATION/ REGULATION	To date, Singapore has not passed any specific legislation or regulation in relation to blockchain technology. In 2016, the Monetary Authority of Singapore ("MAS"): (i) established a "regulatory sandbox" for fintech start-ups to operate in a controlled environment; (ii) prescribed guidelines permitting technology companies to use "the cloud" to offer financial services; and (iii) opened its own innovation lab, called Looking Glass, to experiment with fintech solutions, provide consultation to start-ups, and provide training and facilities for the fintech community. On March 9, 2017, MAS announced the completion of Phase I of an experimental project to conduct inter-bank payments using blockchain technology that it undertook in conjunction with R3, a blockchain technology company, as well as with a consortium of financial institutions including Bank of America Merrill Lynch, Credit Suisse, DBS Bank, The Hong Kong and Shanghai Banking Corporation Limited, J.P. Morgan, Mitsubishi UFJ Financial Group, OCBC Bank, R3, Singapore Exchange, UOB Bank, and BCS Information Systems (which acted as the technology provider to the project). The report "Project Ubin: SGD on Distributed Ledger" released by MAS addresses various issues relating to the usage of blockchain technology in settlement systems. On August 1, 2017, MAS clarified in an announcement that the offer or issue of digital tokens in Singapore will be regulated by MAS if "the digital tokens constitute products regulated under the Securities and Futures Act (Cap. 289) ("SFA") (*see* Jones Day *Commentary*, "Announcement Clarifies Regulatory Position on Digital Token Offerings in Singapore"). Soon thereafter, MAS and the Commercial Affairs Department ("CAD") issued an advisory letter titled "Consumer Advisory on Investment Schemes Involving Digital Tokens," which highlighted what MAS and CAD saw as inherent risks in investments into digital tokens and provided guidance as to what they considered to be a responsible approach for such investments. On October 2, 2017, the Deputy Prime Minister and Minister-in-Charge of MAS reiterated that: (i) "if a token is structured in the form of securities, the ICO must comply with existing securities laws aimed at safeguarding investors' interest"; (ii) money laundering and terrorism financing risks are prevalent when dealing with virtual currencies; and (iii) public awareness of potential scams needs to be highlighted. On May 24, 2018, the MAS released a consultation paper, entitled *Review of the Recognised Market Operators Regime*, which proposed changes to existing regulations in an effort to lower market entry for blockchain-related exchanges. This effort involves expanding the current recognized market operators regime from a single tier to three individual tiers that would more accurately match regulations with the risks posed by certain market operators. The proposed regulations add a tier that is targeted to market operators with limited access to Singapore-based retail investors. They also add an additional tier that is targeted at market operators that have a significantly smaller scale of business compared to more established operators. As an update on Project Ubin, on August 24, 2018, the MAS and the Stock Exchange of Singapore announced a collaboration to develop delivery versus payment capabilities for settlement of tokenized assets across different blockchain platforms.
CASE LAW	On December 27, 2017, in Singapore's first court case involving bitcoin, a Judge in the Singapore International Commercial Court denied plaintiff's summary judgment motion and ordered that the case proceed to Trial. The litigation deals with UK-based B2C2 and the Singapore cryptocurrency exchange Quoine. In May 2018, the MAS warned eight digital token exchanges in Singapore not to facilitate trading in digital tokens that are securities or futures contracts without MAS's authorization. It also warned an initial coin offering issuer to stop an offering of its digital tokens in Singapore, as it had determined that the issuer had contravened the SFA by offering tokens representing an equity ownership in a company without a MAS-registered prospectus.

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Singapore *continued*

KEY LEGAL ISSUES	The general position under Singapore law is that it should be possible to enter into binding agreements and execute those agreements via a blockchain as long as the usual requirements for a valid contract under Singapore law are met—offer, acceptance, intention to create legal relations, certainty of terms, and passing of consideration. Singapore courts generally accept electronic and digital evidence of contracts pursuant to Singapore's Electronic Transactions Act. However, there is no indication (through case law or legislation) at present whether blockchains would be recognized as "property" and, if so, what type of property. There may be a possibility that blockchain technology could be considered to be a chose-in-action. Singapore's courts have cited with approval English case law that defines a "chose-in-action" as something "capable of being turned into money" or that "can only be claimed or enforced by action and not by taking physical possession." Given Singapore's proactive interest in developing the ecosystem of blockchain technologies, it seems likely that Singapore will ultimately support and recognize that assets that exist only electronically may also be considered to be "property."
USEFUL PUBLICATIONS	Monetary Authority of Singapore—"Fintech Regulatory Sandbox in a Nutshell" Monetary Authority of Singapore—"The future is here—Project Ubin: SGD on Distributed Ledger"

JAPAN

OVERVIEW

Japan is particularly active in cryptocurrency and blockchain technology, including actively investing and promoting blockchain platforms and solutions.

In the banking sector, Japanese banks, supported by the Japanese Bankers Association, are engaged in development activities on a common blockchain platform with a view to standardizing blockchain solutions across all banking institutions and significantly lowering transaction costs. These activities include experiments with fund transfers using virtual currencies (as a model for convenient, low-cost, and 24-hour fund transfer service). In addition, a number of Japanese megabanks, notably Mizuho Bank, have built a blockchain-based trade finance platform. In July 2017, for example, Mizuho Bank, Marubeni Corporation, and Sompo Japan Nipponkoa Insurance completed a trade finance transaction between Australia and Japan using blockchain, utilizing a digital platform to complete all trade-related processes, ranging from the issuance of the letter of credit to delivering documents. Looking to leverage their substantial customer bases, Japanese banks also have begun testing operations internally with their own cryptocurrency (such as the MUFG coin of MUFG Bank).

Japan is one of the largest centers of bitcoin trading in the world. With the enactment of the Amended Payment Services Act (discussed below), Japan recognizes the use of bitcoin and other digital currencies as legal methods of payment, and any bitcoin or alternative currency exchange business in Japan must register with the Financial Services Agency of Japan ("FSA") and be subject to strict customer verification requirements. FSA has recently increased oversight of cryptocurrency exchanges due to several recent hacking attacks on certain cryptocurrency exchanges (discussed below).

The Japanese government also has been promoting blockchain technology and is considering the use of DLT in processing government tenders as a first step toward the use of blockchain technology in its digital services. In addition, the Japanese government is considering the use of blockchain technology to upgrade Japan's real estate registration system, so as to enable the relevant authorities more efficiently to collect and manage information on real estate transactions.

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Japan *continued*

LEGISLATION/ REGULATION

There have been recent legislative developments that directly affect the use of blockchain technologies, including digital currencies, in Japan.

- The Amended Banking Act was enacted in May 2017 and came into force on June 1, 2018. The Amended Banking Act, following the accelerating global fintech movement, aims to protect consumers while establishing an institutional framework for promoting open innovation between financial institutions and fintech businesses (innovation through collaboration and cooperation). Specifically, it requires the registration of electronic payment agencies (fintech businesses) and requires financial institutions to make an effort to open access to their systems (through open APIs).
- The Amended Payment Services Act was enacted in May 2016 and came into force on April 1, 2017. The Amended Payment Services Act introduces the registration requirement for operators of "virtual currency exchange businesses" (defined as businesses involving the exchange of virtual currency to legal currency or another virtual currency). Under the Amended Payment Services Act, "virtual currency" is defined as proprietary value not denominated in Japanese Yen or any foreign legal currency that, among unspecified persons, (i) can be used to settle payments for goods and/or services and exchanged with legal currency or (ii) can be exchanged with another virtual currency, and that can be transferred using an electronic data processing system. In addition, in order to prevent money laundering and the financing of terrorism, a registered operator of a virtual currency exchange business will be required to implement certain identity verification procedures, among other steps.

Regulatory authorities have also recently increased oversight of cryptocurrency exchanges.

- On October 27, 2017, the FSA released a statement on ICOs. It clarifies the regulatory position of ICOs under Japanese law and also highlights potential risks to consumers of participating in ICOs.
- On January 26, 2018, Coincheck, a cryptocurrency exchange, was compromised by a hacker. In March of 2018, Coincheck announced that it would begin the process of compensating the 260,000 users impacted by the theft.
- In response to this hack, the FSA investigated Coincheck on February 2, 2018.
- On February 1, 2018, the FSA ordered each of the cryptocurrency exchanges (other than Coincheck) to submit the report on its system risk management system.
- On February 13 and March 23, 2018, the FSA publicized the names of the companies that engaged in a cryptocurrency exchange business without a license.
- On March 8, 2018, the FSA issued orders for business improvement to seven cryptocurrency exchanges, requiring two to halt operations for at least one month due to a lack of necessary internal control systems, embezzlement of customers' assets, and noncompliance with required identity verification procedures. One of the two cryptocurrency exchanges was eventually disabled for engaging in a cryptocurrency exchange business on June 7, 2018.
- In April and June 2018, the FSA further issued orders for business improvement and/or suspension to 10 cryptocurrency exchanges in total, as a result of which almost all of the registered cryptocurrency exchanges were subject to the FSA's order. Three of the cryptocurrency exchanges were ordered to halt operations for two months.
- On September 14, 2018, Tech Bureau, a company that operates a cryptocurrency exchange called "Zaif," was compromised by a hacker. In response to this hack, the FSA issued an order for business improvement to Tech Bureau on September 25, 2018.

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Japan *continued*

LEGISLATION/ REGULATION

In addition, there has been a series of recent governmental and private initiatives relating to the use of blockchain technology in Japan.

- Since March 2017, the FSA has established cooperation frameworks to support innovative fintech companies with financial authorities in several foreign jurisdiction, including the United Kingdom, Singapore, Australia, Abu Dhabi, and Switzerland.
- In September 2017, the FSA established a regulatory sandbox for fintech (Fintech PoC (Proof-of-Concept) Hub) in order to eliminate hesitation and concern that fintech companies and financial institutions are inclined to have in conducting unprecedented tests. The first project using the Hub relates to the construction of an advanced "Know Your Customer" (KYC) platform using blockchain technology, the result of which was announced in July 2018.
- In March 2017, the Japanese Bankers Association ("JBA") published the Report of the Review Committee for the Possibility and the Challenges of Utilizing Blockchain Technology, addressing the potential use and challenges of blockchain technology in the banking sector and recommending a public-private sector joint initiative to address changes in banking operations resulting from the use of blockchain technology. Based on the report, the JBA established a "Collaborative Blockchain Platform," a financial services blockchain technology testbed environment provided to the JBA's member banks.
- In November 2016, the Tokyo Stock Exchange, Inc., Osaka Exchange, Inc., and Japan Securities Clearing Corporation formed a consortium of Japanese financial institutions to conduct proof of concept testing based on past findings and discuss the possibility of applying blockchain or DLT to capital markets infrastructure from both the technical and operational perspectives. Several tests are currently ongoing.

CASE LAW

There are no reported cases on blockchain technology in Japan.

In the bankruptcy proceedings of Mt. Gox, a bitcoin exchange based in Japan, however, the Tokyo District Court ruled that bitcoins are not tangible assets and thus are not subject to the right of segregation (Judgment by the Tokyo District Court on August 5, 2015).

In June 2018, the Tokyo District Court issued an order commencing civil rehabilitation proceedings for Mt. Gox, as a result of which the previously ongoing bankruptcy proceedings were stayed. In bankruptcy proceedings, nonmonetary claims are converted into monetary claims based on the valuation as of the time of the commencement of bankruptcy proceedings. Thus, had the case stayed in bankruptcy court, creditors whose bitcoin holdings were stolen may have been entitled to receiving a only cash payout equal to the value of their holdings in 2014. In the civil rehabilitation proceedings, the creditors may be able to get back a portion of their lost bitcoin holdings.

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Japan *continued*

KEY LEGAL ISSUES	The most notable recent legal and regulatory development relating to blockchain technologies in Japan is the regulation of "virtual currencies" and digital currency exchanges, recognizing the use of bitcoins and other digital currencies as legal methods of payment. As discussed above, all operators of digital currency exchanges must now register with the FSA as payment institutions and meet specified capital, cybersecurity, compliance, and operational requirements and submit to annual audits. There are no special requirements under Japanese law to ensure that smart contracts are valid contracts. Except for certain types of agreements (such as an agreement providing a guarantee), Japanese law does not require any formality in entering into a binding agreement. Although there is no specific law or case law in Japan, it should be possible to enter into binding agreements via a blockchain as long as the usual requirements for a valid contract under Japanese law are met (such as a valid offer and acceptance, etc.). In a civil proceeding in Japan, in principle, there are no limits on the admissibility of evidence except for evidence collected illegally. Further, judges have the discretion freely to evaluate the evidence presented. Although there is no specific law or case law in Japan, records on a blockchain generally should be admissible evidence in a civil proceeding in Japan. Since July 1, 2017, the transfer of virtual currency (VC-cash exchange) is exempted from consumption tax (the Japanese value-added tax) in Japan.
USEFUL PUBLICATIONS	FSA—"Initial Coin Offerings (ICOs): User and business operator warning about the risks of ICOs" IMF—"IMF-JFSA-BOJ Conference on Fintech" Deloitte—"Verification report on KYC advanced platform utilizing blockchain technology by the Blockchain Study Group" Japanese Bankers Association—"Report of the Review Committee for the Possibility and the Challenges of Utilizing Blockchain Technology" Tokyo Stock Exchange press release—"Launch of Consortium and Proof of Concept Testing for Capital Market Infrastructure Utilizing Blockchain Technology"

AUSTRALIA

OVERVIEW

The Australian government has publicly stated an intention for Australia to be a leader in the development and use of blockchain and other distributed ledger technologies. It has been working with Data61, the digital and data innovation arm of the Commonwealth Scientific and Industrial Research Organization ("CSIRO"), to deliver two reports on the regulatory, technical, and social implications of blockchain technology in Australia. The first report, titled "Distributed Ledgers, Scenarios for the Australian economy over the coming decades," investigates possible uses of blockchain technology in Australia in 2030. The second report, titled "Risks and opportunities for systems using blockchain and smart contracts," examines how blockchain systems can more immediately support new markets and business models.

Australia is also a leader in blockchain standards. In late 2016, the International Organization for Standardization supported a proposal for Standards Australia, the peak standards organization in Australia, to develop new international standards on blockchain. This would be achieved by the establishment of a new technical committee, responsible for supporting innovation and competition by introducing these international standards. In September 2016, ISO announced that Australia would manage the Secretariat of the new technical committee (ISO/TC 307), which led to Australia hosting the first international blockchain standards meeting for ISO/TC 307 in April 2017.

Standards Australia has also published its "Roadmap for Blockchain Standards" Report, which is designed to identify technical issues associated with developing, governing, and utilizing blockchain and distributed ledger technologies, identify blockchain and distributed ledger technologies use-cases relevant to Australia, and prioritize the order of standards development activities that could be undertaken in the development of blockchain standards by ISO/TC 307

Although Australian regulators have, with some exceptions, been generally reluctant to make definitive or concrete rulings or assessments, the Australian financial services market is highly regulated, and there is potential for the use of blockchain technologies by market participants to be subject to regulation by several different agencies.

In addition, in January 2016, the Australian Securities Exchange ("ASX") invested in, and engaged a, U.S.-based firm ("Digital Asset") to develop solutions for the Australian equity market using DLT.

In particular, ASX intends to replace the system currently used for post-trade processing, clearing, and settlement of equities, CHESS, with a post-trade platform that utilizes DLT to enable significantly faster settlement of equity transactions. In April 2018, ASX released a detailed consultation paper in relation to the proposed replacement of CHESS and confirmed that the new DLT system is currently estimated to commence operation sometime between Q4 2020 and Q1 2021. In September 2018, ASX published its response to the stakeholder feedback it received and outlined changes ASX will be making to its scope and implementation plan as a result of that feedback.

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Australia *continued*

LEGISLATION/ REGULATION

On April 3, 2018, the Australian Transaction Reports and Analysis Centre ("AUSTRAC") introduced amendments to the Anti-Money Laundering and Counter-Terrorism Financing Act 2006 to include regulation of digital currency exchange providers in Australia. The effect of the amendments are that digital currency exchanges are subject to the same anti-money laundering and counter-terrorism financing laws as institutions that deal in fiat currency, such as banks. This includes adopting an AML/CTF program to identify, mitigate, and manage money laundering and terrorism financing risks, identifying and verifying the identities of their customers and reporting to AUSTRAC suspicious matters. Businesses will also be required to register with AUSTRAC to be able to provide digital currency exchange services. There are criminal and civil penalty consequences for providing digital currency exchange services without being registered.

The Australian Securities and Investments Commission ("ASIC"), which is the federal body primarily responsible for regulating corporate and financial services businesses, has, however, expressed a willingness to engage with stakeholders in regulating the use of the technology. Its position is that the current regulatory framework already requires financial services businesses to have appropriate technological resources and risk management systems, and that at this stage no further framework is required.

ASIC has also published an information sheet (INFO 219) for entities considering operating market infrastructure, or providing financial or consumer credit services, using distributed ledger technology or blockchain. The information sheet allows companies to determine whether their use of distributed ledger technology falls within ASIC's regulatory requirements by providing a framework of six questions that can be asked by a blockchain user:

1. How will the blockchain be used?
2. What blockchain platform is being used?
3. How is the blockchain using data?
4. How is the blockchain run?
5. How does the blockchain work under law?
6. How does the blockchain affect others?

ASIC has also developed an assessment tool for business seeking to utilize blockchain to assist them in evaluating whether they fall under ASIC's regulatory requirements. This tool can be found at Appendix 1 to INFO 219.

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Australia *continued*

LEGISLATION/ REGULATION	Regulatory agencies in Australia have taken several other steps in regulating or monitoring the use of blockchain technology: • ASIC established an "Innovation Hub" in 2015 to assist financial technology start-ups navigate Australia's regulatory system by providing "informal guidance" to eligible businesses. • The Australian Transaction Reports and Analysis Centre ("AUSTRAC") has recommended both a high-level regulatory framework and a set of agreed rules that determine the operation of the algorithms encoded by the software for the use of blockchain. • AUSTRAC has also made it clear that financial institutions' obligations under Australia's anti-money laundering and counter-terrorism financing legislation do not require the closure of bitcoin-linked accounts deemed to be high-risk, despite indications that some financial institutions have already done this in response to perceived regulatory pressures. • AUSTRAC also reminded exchanges to enroll in the "Digital Currency Exchange Register," maintained by AUSTRAC by May 14, 2018. These "transitional registration arrangements" allow operators to continue business while having their applications screened. AUSTRA also issued a warning in April of 2018, stating that "there will be criminal offence and civil penalty consequences if you provide digital currency exchange services without being registered." • The Australian Taxation Office ("ATO") has released a guidance paper titled "Tax treatment of crypto-currencies in Australia," which provides the ATO's view that crypto-currencies such as bitcoin are neither a domestic nor a foreign currency, and are instead assets, and that transacting with bitcoin is "akin to a barter arrangement." • The Australian Competition and Consumer Commission ("ACCC") has been closely monitoring the acquisition of blockchain start-ups by banks, due to their disruptive nature to the industry, and it has also indicated that banks may need to seek ACCC permission before entering into agreements to cooperate with blockchain start-ups. • In September of 2018, The Australian Trade and Investment Commission (Austrade) and the Australian Digital Commerce Association jointly organized a delegation of domestic Blockchain startups to visit China's largest fintech companies.
CASE LAW	There are no cases on the legal issues surrounding blockchain technology in Australia
KEY LEGAL ISSUES	The key legal issue in Australia is the significant number of regulatory hurdles that financial technology and financial entities may be required to jump in order to develop and utilize blockchain or distributed ledger technology. The financial services industry in Australia is currently regulated by ASIC, the Reserve Bank of Australia, the ATO, the ACCC, the Office of the Australian Information Commissioner, AUSTRAC, the Digital Transformation Agency, and the Australian Prudential Regulation Authority. Each of these bodies has the power to regulate the use of blockchain in Australia, and although regulators have, with some exceptions, generally avoided making definitive statements or rulings, the extent of these powers is not yet clear should they adopt a more heavy-handed approach. In fact, ASIC's information sheet INFO 219 advises that these other regulators may also be interested in a business or proposal.
USEFUL PUBLICATIONS	CSIRO Report—Distributed Ledgers, Scenarios for the Australian economy over the current decades CSIRO Report—Risks and opportunities for systems using blockchain and smart contracts ASIC Information Sheet—"Evaluating distributed ledger technology" Standards Australia—Roadmap for Blockchain Standards Report (March 2017) AUSTRAC information—"Are you a digital currency exchange provider?" AUSTRAC information—"New Australian laws to regulate cryptocurrency providers"

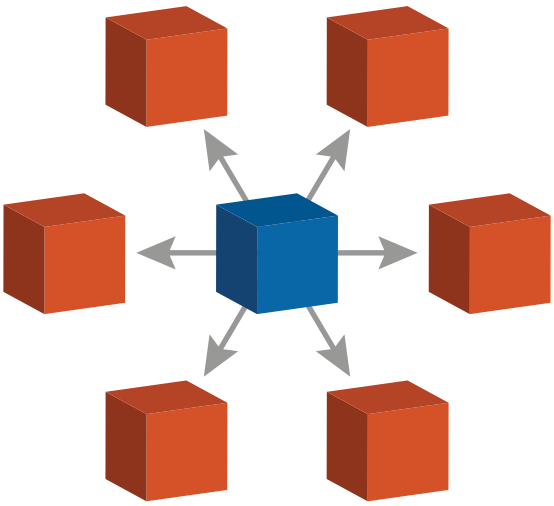
APPENDIX

THE TECHNOLOGY BEHIND BLOCKCHAIN

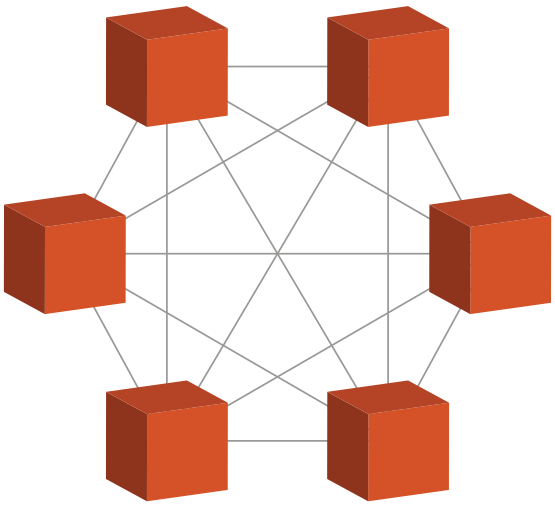
Blockchain is a technology for storing, tracking, and processing information. At its simplest, a blockchain is a digital database of transactions. Each transaction is stored in a block of data that is securely linked to the blocks containing previous and subsequent transactions. What makes blockchain technology so interesting and potentially powerful for business transactions is the characteristics that flow from this digital chain of transactions.

Information is "Distributed"

Centralized System



Distributed System



Today's information systems are typically centralized. That involves one or more central intermediaries (such as a bank) responsible for transferring actual value between two parties. Each party will maintain its own separate ledger recording every transaction, but this is normally not the authoritative ledger (which remains with the central counterparty). For every transaction, the two parties and the central intermediary need to each update and then reconcile their own ledgers. If a party loses its ledger due to an IT failure, malware attack, or physical disaster, there is a risk of loss of information due to the single point of failure.

In contrast, a blockchain system is decentralized or distributed. That means that each user of the system has its own authoritative copy of the digital transaction record where it records every new transaction among group participants. This is why distributed ledger systems are sometimes referred to as "trustless," because they can be designed in such a way that nobody has to trust in a central party or anybody else in order for the system to function.

New transactions are immediately replicated onto all ledgers at the same time, meaning that no single point of failure exists in the system. Thus, blockchain systems have a significant advantage on standard systems, even where there is only one "user" (for example a global company tracking inventory via a blockchain system).

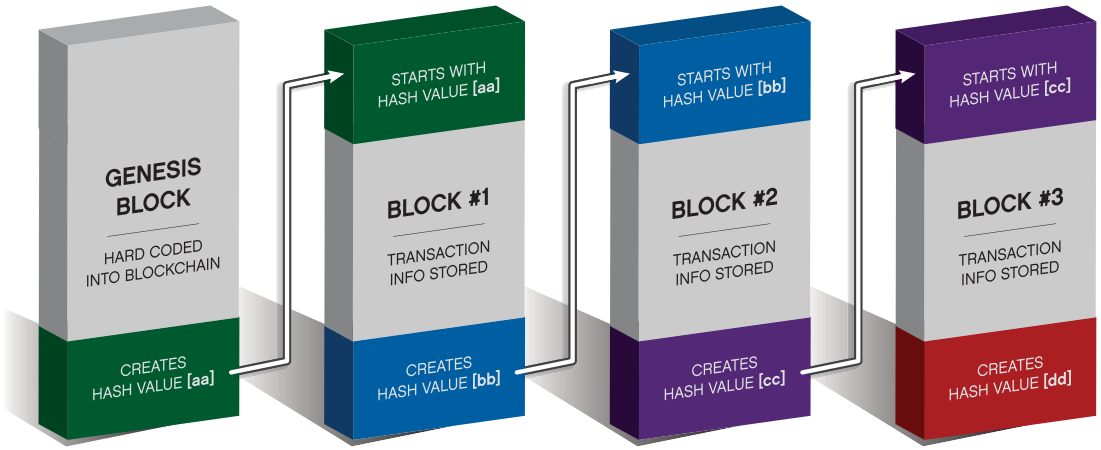
It is important to understand that blockchain systems can be set up with a variety of different controls and access rights. It is possible to set up a blockchain in an open way, so that any third party can access it—similar to setting up a website that can be accessed by any internet user. A much more common approach for business is to set up a permissioned blockchain, so that only certain users can access it—similar to setting up a private intranet.

A blockchain can also be set up with a main administrator, if required. Even in this case, the digital record is much harder to hack, manipulate, or be disrupted in the same way as a database stored on a single computer or server because of the way that information replicates, making it a more robust system for information storage.

Information is "Immutable"

Distributed ledger technologies provide an "immutable" record—blocks of data are added in a linear and chronological order, each linked backward and forward to prior and subsequent transactions by a cryptographically secure, digital fingerprint, created using a hash function. In basic terms, the record of each transaction cannot be changed once it is added without disrupting the line of digital fingerprints, providing an audit trail and significant certainty as to the status of each transaction on the record.

Representation of blocks in a ledger



If you change any of the information in blocks #1, #2, or #3 after the block is created, the hash value at the bottom of the block and the start of the next block will be different, evidencing that the record has been tampered with.

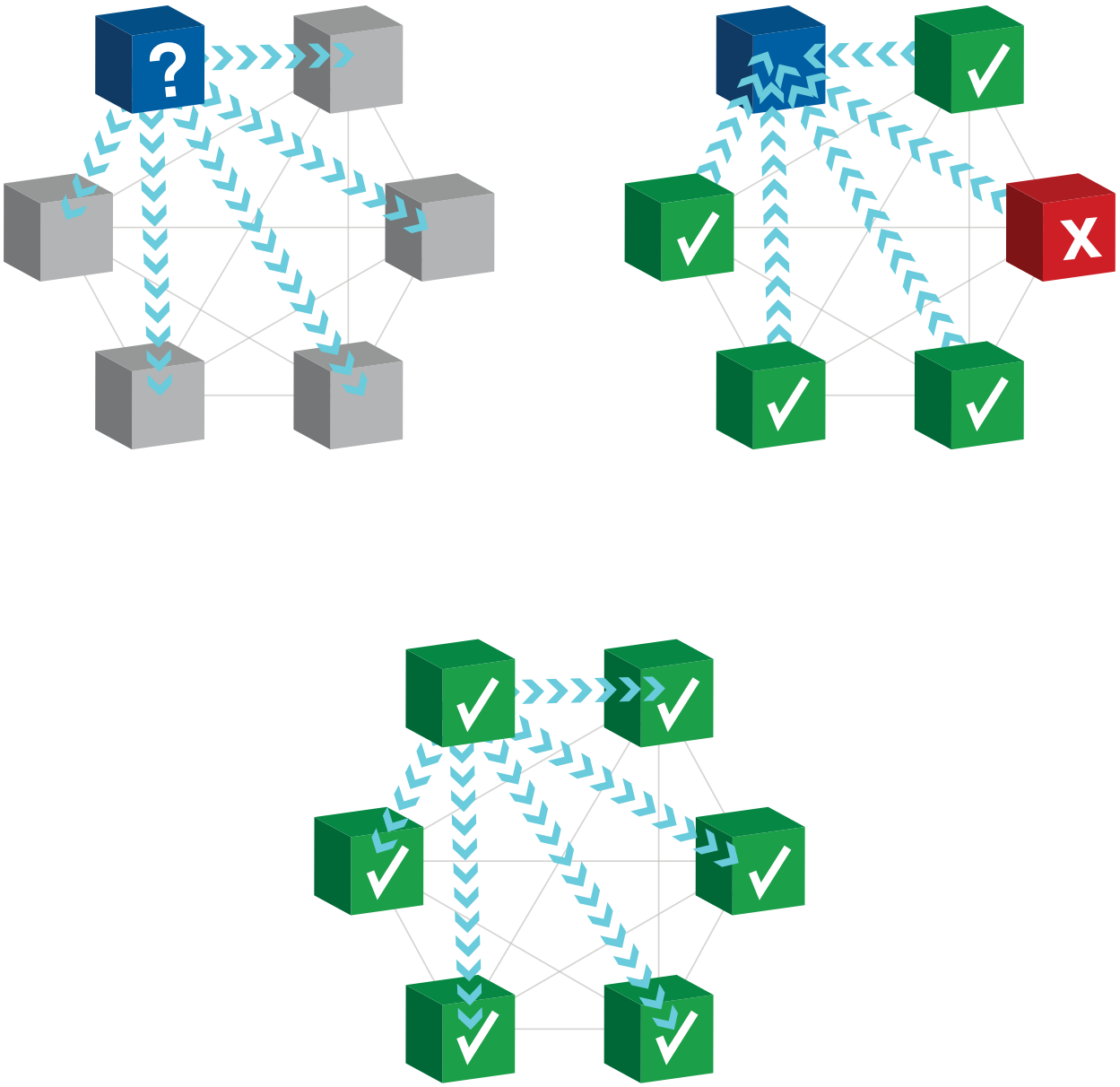
Transactions are Approved by "Consensus"

Distributed ledgers can be set up in different ways, but a common feature is "consensus"—a transaction will be approved and added to the digital record when a sufficient number of participants on the network agree that the transaction should be added using an agreed mechanism. Precise consensus mechanisms are highly technical and vary between different use cases, but they consist of the rules for how every user exchanges blockchain information, the mathematical rules for all users to agree on the integrity of that data (sometimes called "proof of work"), and sometimes an incentive to support the consensus model.

Consensus is the agreed method to ensure all transactions are validated and all valid transactions are added once and only once. Importantly, valid transactions also cannot be declined or omitted from the blockchain.

A basic example of a consensus mechanism is below:

In this diagram, one user wants to enter into a transaction on the ledger. He or she broadcasts a block containing the transaction data to everyone else in the network. If a sufficient number of users confirm the transaction complies with the rules of the distributed ledger (here, 50 percent + 1 users agree that the rules have been complied with), the transaction will be "approved" and added to the ledger as the next block in the chain, even for the user who did not approve the transaction.



Smart Contracts and Smart Assets

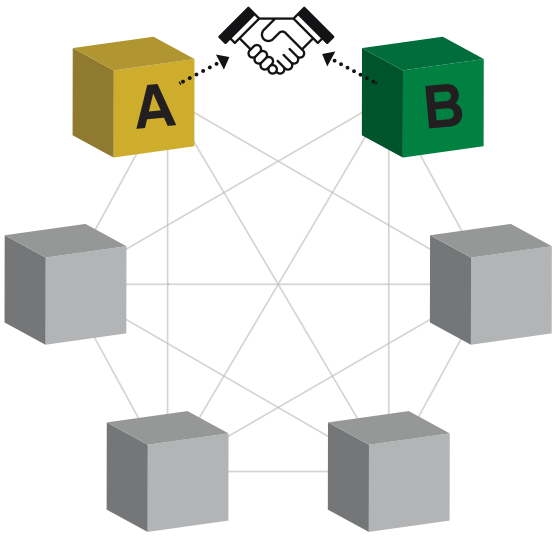
Distributed ledgers can use smart contracts to execute automatic transactions in respect of assets whose ownership is recorded on the ledger (smart assets) without the need for human intervention or an intermediary to monitor or manage the transaction.

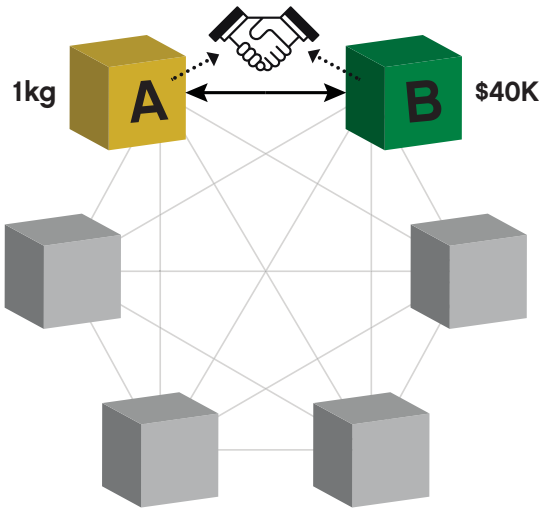
A smart contract is a piece of computer code using standard logic terms. When a user stores value from tangible assets (cash in a bank account or shares he or she owns, for example) on a distributed ledger, it is possible to implement a smart contract that then automatically transfers that value to another participant on the occurrence of certain events or on a pre-agreed basis.

A and B are users on the same distributed ledger

They enter into smart contract based on price of gold.

Terms are that A agrees to sell 1 kg of gold to B at the prevailing USD spot price at a particular day/time, but only if the spot price is greater than $40,000 at that time.





Smart contract would use the following logic –

- On Day/Time, OBTAIN Spot Price.
- IF Spot Price >$40,000 then TRANSFER 1 kg of gold from A to B
- TRANSFER $x from B to A WHERE x = Spot Price amount for 1 kg of gold in US Dollars at Day/Time.

LAWYER CONTACTS

Jones Day has been advising on the implementation of blockchain technology since 2015 across a range of sectors, including obtaining the first-ever effective SEC registration statement that contemplates a public offering utilizing blockchain technology, for Jones Day client t0.com, Inc.

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CENTER for Supply Chain Studies™

ReferenceModel-based Exploration and Education

The Drug Supply Chain Security Act and Blockchain

A White Paper for Stakeholders in the Pharmaceutical Supply Chain

June 21, 2018

www.C4SCS.org

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Introduction

The 2013 Drug Supply Chain Security Act (DSCSA) prescribes a set of compliance requirements for pharmaceutical supply chain participants over a ten-year period (2013-2023). Most notably, it requires manufactures of pharmaceutical products sold in the U.S. to serialize, or uniquely identify, pharmaceutical products at the lowest saleable level. Additionally, all supply chain participants must share certain product, production, trading partner and ownership change data.

Of importance to the industry is that in 2023, "interoperable, electronic tracing of product at the package level requirements shall go into effect".[1] Some have interpreted this to mean supply chain participants are required to put in place an **electronic system to facilitate the collection of information** for all current and previous changes of ownership (*leading back to the original manufacturer or repackager*).

Specifically, the DSCSA calls for:

- Exchange of Transaction Information (TI) and Transaction Statement (TS)
- Systems and processes for verification of product at the package level
- Systems and processes necessary to promptly respond with the TI and TS information
- Systems and processes necessary to promptly facilitate the gathering of information to produce the TI going back to the manufacturer
- Ability to only accept saleable returns for products that they can associate to the TI and TS

There are concerns that retrieving TI data back to the manufacturer could require tens of thousands of electronic connections between previously "unconnected" participants. Essentially, each supply chain participant might need to form an electronic connection with each potential company participating in their supply chain. *Currently, no such electronic system exists.*

Blockchain technology has demonstrated a strength in creating a single source of truth that is highly resistant to corruption – either accidental or intentional. It also holds promise for being able to restrict access to competitively valuable transaction data only to those parties with a defined "need to know," providing the confidentiality sought by trading partners.

Current blockchain platforms offer an environment of simplified electronic connections between parties for data distribution, synchronization and immutability, programmability, visibility, security and potentially, confidentiality – all characteristics of an effective environment where trading partners can enforce business and regulatory rules and securely automate the exchange of data. *(It should be noted that the language of the DSCSA calls for transaction data exchange to be interoperable. In some quarters this is seen as being different than an interoperable system.)*

In this highly complex and regulated industry,
the Study Team explored if blockchain technology can be used
to address the full data sharing requirements of the DSCSA.

[1] H.R. 3204 Title II – Drug Supply Chain Security Act: Sec. 203. (g) Enhanced Drug Distribution Security

DSCSA and Blockchain Study

Overview

This white paper provides insights into the team's process, exploration and learnings throughout the Study. Future teams will build upon the learnings of this group and take the next steps of building proof of technology, proof of concept, pilots and extensions on the basic DSCSA data set used in this work.

Building the team, setting the goals.

In the winter of 2017, a group of regulatory, operations, clinical, I.T. and other backgrounds from 50 healthcare industry stakeholder companies and associations came together as a team to explore the use of blockchain technology to support Drug Supply Chain Security Act (DSCSA) compliance and to add additional value.

Considering the requirements of the DSCSA and the current state of data sharing in the industry, the team established a list of goals to address during the study that were considered important for the industry to be able to support DSCSA compliance in 2019 and 2023.

The list included:

- Establishing an electronic connection between non-adjacent trading partners
- Establishing trust between these trading partners
- Sharing required data without inadvertently exposing proprietary information
- Reducing the potential activity required of trading partners
- Designing for expansion beyond DSCSA compliance
- Funding the architecture
- Reducing risk

Together, the team established a framework for holding exploratory discussions (described later in this paper). This outline structure allowed the team to consider governance, technology, services and supply chain practices clearly and distinguish between DSCSA requirements, supply chain needs and individual trading partner pair agreements. Initial talks served to establish a level of knowledge among team members on the complex topics of the DSCSA, supply chain practices and blockchain technology.

Next, we created various exploratory designs (or models) in which these three complex topics might be brought together to aid in DSCSA compliance and adding additional value. These designs were cast into simulated ReferenceModels™[2] to enable the team to exercise some of the data sharing rules and explore potential data outputs.

[2] ReferenceModels™ are key to the Center's Study process. They are computer simulations and diagrams of the supply chain and supply chain stakeholder interactions that explore various design alternatives, regulation interpretations, future states and technology usage. They also help Study teams to animate, test and evaluate a current or proposed scenario.

The U.S. Pharmaceutical Supply Chain

The role of the trading partners.

Like most of today's mature supply chains, the U.S. pharmaceutical supply chain contains many types of trading partners, as well as the companies who support them with logistical and data services solutions.

Trading partners are highly controlled by various regulatory bodies and certifying agencies. Caution must be taken when contemplating any type of change as new requirements may impact existing regulatory or certification rules. Often, in our discussions of DSCSA-related process changes, stakeholders advised us of existing requirements that needed to be taken into consideration.

An example of this is the DSCSA requirement that a trading partner cannot receive product without also receiving proper DSCSA mandated information. In the case of a temperature sensitive drug, for instance, there are also requirements that the drug be placed in a temperature-controlled environment to maintain the efficacy of the drug.

Defining the Study parameters.

These and many other requirements lead to further conversations on the accuracy of process and data definition to avoid conflicting with one rule while attempting to comply with another. The Design Models discussions helped clarify current and proposed process controls and practices and explore the impact of laws, regulations and technology on the supply chain and individual trading partners.

The team tackled new challenges as it worked through DSCSA definitions and requirements of supply chain participant types and the (sometimes) multiple roles that the trading partners perform. To clearly address these issues and allow for typical supply chain behavior and individual trading partner agreements, the team assigned ReferenceModel rules into these three categories:

1. **DSCSA:** The rule can be directly linked to language in the DSCSA
2. **Supply Chain:** The rule exists due to established practices and trading partner needs
3. **Trading Partner Agreements:** Recognizing that trading partners can choose to share additional data based on their individual business arrangements

Defining these rules allowed the team to have targeted, exploratory discussions on several topics without blurring the lines between what is specifically called for in the law and what may be desired or needed by trading partners. They also helped us in establishing ReferenceModel runs that tested whether data created in a trading partner to trading partner agreement can successfully be held confidentially in the shared industry blockchain.

The Drug Supply Chain Security Act[3]

The Drug Supply Chain Security Act (DSCSA) contains a vast array of requirements to be implemented over a ten-year period (2013-2023). The Study concentrated on requirements that the supply chain must comply with by the year 2023 and all previous requirements that will still be in effect then.

Specifically, the team focused on a scenario where all required finished drug products are serialized (are marked with a 2D barcode containing the NDC (GTIN), Serial Number, Lot Number and Expiration Date), trading partners are required to share Transaction Information (TI) and Transaction Statement (TS) and where trading partners have *"The systems and processes necessary to promptly facilitate gathering the information necessary to produce the transaction information for each transaction going back to the manufacturer, as applicable."*

When the law was drafted, there were expectations that all DSCSA defined data would be included in a single "document". The Study team took the point-of-view of a trading partner – able to collect all the data from appropriate sources and coalesce the data into a "document" if needed. This strategy falls within existing master data management practices and efficient storage practices.[4]

A note on the DSCSA Transaction Statement:

The Transaction Statement is a series of attestations that the transferring trading partners are required to make to those trading partners with whom the product is being sent. These include confirmations that the product was purchased directly from the manufacturer, exclusive distributor of the manufacturer, or repackager that purchased the product directly from the manufacturer when that purchase occurred. Trading partners have been making these attestations either by including the specific language of the DSCSA or by reference. In February 2018, the FDA issued a Draft Guidance allowing for a shortened attestation.

All ReferenceModels developed by the Study Team assume that a shortened attestation would be allowed and that further, an automated means of attestation may be allowed. This could be an indicator in the TI data set could be set, or an attestation that any post to the system would constitute attestation that the posting body has complied with the language in the law. As a result, the ReferenceModels described in this white paper do not address Transaction Statement requirements.

[3] https://www.fda.gov/drugs/drugsafety/drugintegrityandsupplychainsecurity/drugsupplychainsecurityact/default.htm

[4] See Center's Study on DSCSA and MDM: https://c4scs.org/s/White-Paper-DSCSA_MDM_Center-for-Supply-Chain-Studies_FINAL.pdf

Blockchain Technology

Wikipedia defines blockchain as:

> "A **blockchain**, originally **block chain**, is a continuously growing list of records (Figure 1), called *blocks*, which are linked and secured using cryptography. Each block typically contains a cryptographic hash of the previous block, a timestamp and transaction data. By design, a blockchain is inherently resistant to modification of the data. It is "an open, distributed ledger that can record transactions between two parties efficiently and in a verifiable and permanent way". For use as a distributed ledger, a blockchain is typically managed by a peer-to-peer network collectively adhering to a protocol for inter-node communication and validating new blocks. Once recorded, the data in any given block cannot be altered retroactively without the alteration of all subsequent blocks, which requires collusion of the network majority."

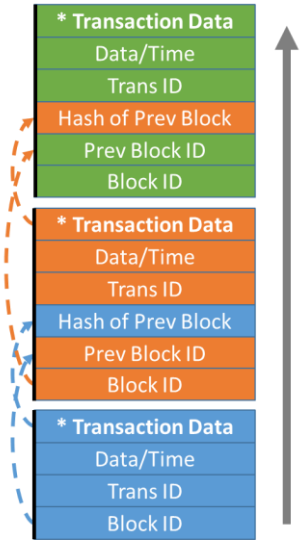

Figure 1: *Blockchain*

Key observations of blockchains

- By design, inherently resistant to modifications of data *(data is said to be immutable)*
- They are utilities upon which business applications can be built
- They distribute data securely and ensure all copies are identical
- Each process may be assessed a fee *(may be key to funding industry shared blockchains and as a deterrent to nefarious activity)*
- They are programmable using distributed applications (DApps), sometimes known as Smart Contracts *(could be used to enforce industry and regulatory rules)*
- The DApps are also visible, immutable and distributed
- Correctly developed DApps can be verified and their output predicted and trusted

Many blockchain platforms[5] incorporate the concepts of blockchain and additional capabilities based on the types of uses anticipated. For the purposes of this Study, we did not assume the use of any one. Instead, we explored and simulated the capabilities available in many popular platforms:

- Data is "write only" *(cannot be changed or deleted once posted to the blockchain)*
- Data may be visible to all parties connected to the blockchain
- Full copies of the blockchain data may be distributed to all blockchain nodes
- Distributed applications *(which trading partner systems can interact with)* can access and act on data stored on the blockchain
- Distributed applications can enforce data access and certain data quality rules *(such as data format)*
- Use of special applications (oracles) that can access information that resides outside (off) the blockchain

[5] Article on different blockchain platforms: https://medium.com/blockchain-blog/17-blockchain-platforms-a-brief-introduction-e07273185a0b

The team also explored and discussed features that are implemented in a few blockchain platforms and are envisioned to be available in the future, including:

- Substantial data storage located off the blockchain, yet accessible to the blockchain and distributed applications on the blockchain
- Indexing of blockchain data to enable querying and retrieval
- Data obfuscation *(blockchain platform features to obfuscate data and retain query features)*

Standards usage

Unique Identification, Data Attribution, Process Controls, Labeling and other standards are foundational to sharing data and provide the ability to simplify business transactions, improve efficiencies and reduce risk. They allow innovations to be accepted and incorporated into existing practices with the least amount of overhead or customization. All ReferenceModels created in this Study make use of appropriate standards such as identification, transaction, data and process.

Specifically, the ReferenceModels made use of these standards:

GS1 Identifiers

- Global Trade Item Number (GTIN)
- Serialized Global Trade Item Number (SGTIN)[6]
- Lot Global Trade Item Number (LGTIN) [7]
- Serial Shipping Container Code (SSCC)
- Electronic Product Code (EPC)

GS1 Traceability Standards

- Electronic Product Code Information Services (EPCIS)
- Core Business Vocabulary (CBV)
- Tag Data Standard (TDS)

GS1 Data Definitions

- Global Data Dictionary

GS1 US DSCSA related attributes and EPCIS usage

- GS1 US Implementation Guideline: Applying GS1 Standards for DSCSA and Traceability

[6] GS1 Tag Data Standard version 1.9: The SGTIN is a EPC URI syntax and is composed of a GTIN and a serial number

[7] GS1 Tag Data Standard version 1.9: The LGTIN is a EPC Class URI syntax and is composed of a GTIN and a Lot Number

Concepts

Industry-Shared Blockchain (ISB)

Although some individual solution providers may use a blockchain platform for their service, the Industry Shared Blockchain (ISB) refers to the platform(s) that connects all individual services. The Distributed Logic in the ISB is the result of industry stakeholder consensus and is available for those stakeholders to validate.

Connecting to the blockchain through a Service Provider

A supply chain participant looking to establish an electronic connection with others would first register with a service connected to the ISB. That service will ensure the company is assigned a proper identity on the blockchain and fulfills its obligations in terms of initial setup such as identification of products and establishment of them on the ISB *(for ReferenceModels where this is required).*

Confidentiality

A process by which data is only shared with appropriate trading partners. Regarding DSCSA, this means that each trading partner should be able to access Transaction Information (TI) for items they have or are about to take ownership of. They should be able to access TI for the exchange in which ownership is transferred to them and all previous transfers within the supply chain. Trading partners should not have access to TI of items or shipments for which they never had ownership. Exceptions to this rule are 3PLs who do not take ownership but are required to have access to TI for shipments of which they previously had custody.

Scenarios

Although there are many nuanced scenarios that take place within the supply chain during the life cycle of a pharmaceutical product, these are the scenarios discussed throughout the study to determine the potential role of blockchain technology.

Transfer of product between trading partners

In this basic scenario, items are transferred from one trading partner to another without error. Party 1 commissions and packages the items and ships to Party 2. Party 2 receives the items, verifies that the items received were placed into commerce by the manufacturer (commissioning took place) and prepares them for the next step (storage, unpacking and repacking for shipment, dispensing). A series of trading partners can be linked together to vary the scenario.

Saleable return

The receiving trading partner (Party 2) returns product to the sender (Party 1). Party 1 verifies that ownership of the returned item was originally transferred from Party 1 to Party 2. Party 1 also verifies that the items were placed into commerce by the manufacturer and that there is no other information to indicate that the items should not be treated as saleable product.

Non-saleable return

The receiving trading partner (Party 2) returns product to the sender (Party 1). Party 1 verifies that ownership of the returned item was originally transferred from Party 1 to Party 2. Party 1 also verifies that the items were placed into commerce.

In this scenario, Party 1 finds the items are not saleable (expired, recalled, damaged, etc.). Party 1 then either returns the items to the party they received them from (manufacturer or another wholesaler) or transfers them to a Returns Processor (Party 3). Party 3 destroys the product and provides information of the destruction to the manufacturer.

Delayed information availability

Items are transferred from one trading partner to another without error. The Manufacturer (Party 1) commissions and packages the items and ships to Party 2. However, Party 1 processes their information in batches and the Transaction Information (TI) becomes available several hours after the shipment arrives at Party 2. Party 2 secures the product, indicates that the TI is not available and processes the items up to the point of shipment or use. Prior to shipment or use, Party 2 must verify that TI from Party 1 is available and that the item was placed into commerce by the manufacturer (commissioned).

Hospital Pharmacy Borrow and Loan

A hospital requires a drug that is either not available or may be costly and seldom used. The hospital arranges to borrow a quantity of the drug from another local hospital. The borrowing hospital may, or may not, know the patient (e.g., a previously admitted patient or a newly arriving patient). The borrowing hospital acquires the drug from the lending hospital and replaces the drug once they acquire new stock of the drug.

Exception processing

Errors do occur. Logistics units are sometimes packed incorrectly, shipments arrive at the wrong destination, etc. Discrepancies between what took place and what was *recorded as taking place* need to be corrected.

A key feature of blockchain technology is data immutability. On most ledgers, entries are corrected by posting offsetting entries. The Study team explored this concept and found that it could lead to misunderstandings when attempting to replay and understand a series of transactions. Instead, it employed a simple “replace” mechanism by indicating that the corrective transaction replaces a previous (erroneous) transaction. This works for most cases and only is an issue when the desired effect is to have a transaction ignored (it was in error, won’t be replaced and needs not to be part of any transaction set analysis). An efficient method of correcting information in an immutable dataset remains a challenge.

Challenges

The Study team explored challenges regarding the complexity of the DSCSA statute and interpretation, the nuances of Supply Chain practices and the ever-evolving blockchain technology and platforms. *A few of the challenges included:*

The Drug Supply Chain Security Act (DSCSA)

Multi-link transactions:

Most transactions (ex: orders, invoices, payments, etc.) in business are [8]between two trading partners. The DSCSA requires *(depending on your interpretation)* sharing certain data with the entire list of trading partners responsible for transferring packages to the dispenser. For the purposes of this Study, transactions were recorded at the smallest saleable package level.

SEC. 203(g)(1)(E) of the DSCSA:

Retrieving previous Transaction Information going back to the manufacturer. *For example*: in Figure 1 below, the hospital may be required to retrieve TI^1 and TI^2. These transactions contain data (ship dates, quantities, etc.) that is confidential between the transacting trading partners. For the purposes of this Study, confidential data from previous transactions were redacted or removed when shared with trading partners who were not parties to the transaction.

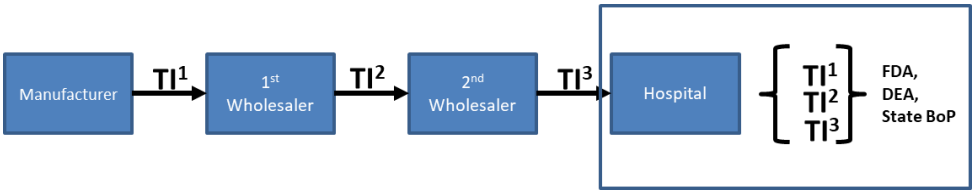

Figure 2:
Transaction Information sharing

2019, Verification of saleable returns:

Beginning in November 2019, the DSCSA requires wholesalers to verify that the manufacturer placed the Product Identifier (PI)[9] in commerce for packages returned that the wholesaler determines are saleable. This is a challenge to the wholesalers as, by this date, packages will be marked with the Product Identifier. However, manufacturers are not required to transmit the product identifiers in the TI until November 2023.

The result is the need for a system that enables wholesalers to request verification of the PI and for manufacturers to provide verification. This system may not be needed in 2023 when manufacturers will begin to pass the PI in the TI and wholesalers will have the information to verify saleable returns.

[8] https://www.fda.gov/drugs/drugsafety/drugintegrityandsupplychainsecurity/drugsupplychainsecurityact/default.htm

[9] The DSCSA defines the Product Identifier as the National Drug Code (NDC), Serial Number, Lot Number and Expiration Date. In practice, the NDC is imbedded in a Global Trade Item Number (GTIN), a product identification standard of the GS1 standards body.

The Supply Chain

Multiple company identifiers:

The DSCSA requires that TI and TS be shared between trading partners upon the change of ownership. Changes in product location (i.e. a change of custody) may not always cause a change in ownership in activities such as intra-company transfers or transfers using a third-party logistics provider (3PL), and do not require TI and TS to be shared.

Study scenarios were constructed under the assumption that companies will use their corporate identification to document change of ownership. However, some States require transacting companies to be licensed in the State. This may require an implementation where one (corporate) blockchain account ID be associated with more than one transacting entity ID to correctly discern transactions that were made between divisions of the same company and between separate trading partners. Incorporating the use of company hierarchy repositories such as GS1 Global Location Number repositories could support this distinction between federal and state law.

Data access governance:

Who sees what data when? This is partially addressed in the DSCSA statute itself. Typical transactions (orders, invoices, ship notices, etc.) pass between two trading partners. In the DSCSA requirements, certain data is passed serially from one trading partner to another. Lot numbers, expiration dates, etc., make up the Transaction Information (TI) that each trading partner must make available to their customers.

Ensuring that TI data is accessible to only those in the supply chain that have, or have had, ownership of the package may require a choreography of digital signature exchange, clever encryption and or other methods being investigated such as zero knowledge proofs[10].

Blockchain

Obfuscating data on the Blockchain:

As data on most of today's blockchain platforms is visible to all connected parties, it is necessary to obfuscate confidential data stored on the blockchain. Also, as the DSCSA is a traceability-only law, prior trading partners should not be able to un-obfuscate data authored by future trading partners. In the end, there is very little if any data that can remain un-obfuscated on the blockchain.

Confidentiality can be attained in several ways:

1. Access to the data can be limited by rules that are hard coded into the blockchain software and that are implemented in rigidly enforced operational processes.
2. The data itself can be encrypted and the decryption keys carefully managed to limit its use to approved parties. Unfortunately, encrypted data becomes difficult to query.

[10] A **zero-knowledge proof** or protocol allows a "prover" to assure a "verifier" that they have knowledge of a secret or statement without revealing the secret itself.

3. Various obfuscation techniques can be employed that obscure certain data items (notably, the identify of trading partners) without limiting the ability of approved parties to selectively query the database.

4. A data architecture can be crafted that keeps humans from seeing the data once it has been validated by the transacting parties. Maintenance of the blockchain consensus can be maintained by machines without intervention (other than independent auditing). The information that is required to be passed on can be generated by reports. *This fourth option was not investigated in the Study.*

The team experimented with a few mechanisms to obfuscate the data including encrypting the data[11], digitally signing[12], storing only hash values and zero knowledge proofs as a mechanism to protect data. Encryption and signing introduce additional steps of exchanging keys and key management into the overall data exchange and storage process.

We found that encryption of the product and trading partner identifiers itself was not enough to protect against parties who might examine large volumes of transactions, often looking for and matching patterns to aid in discerning who the trading partners were or what the product being transferred was.

We then explored using the full PI (GTIN, Serial Number, Lot Number and Expiration Date) to create enough differentiation and rely on the barcode as the mechanism to transfer knowledge of the PI. This produced a less "guessable" encryption. However, this encrypted value would also be identifiable for each transaction in which the item occurred. The need for an additional data value that changed with each transaction created an encrypted value that was not repeated across transactions. This also produced data that was not searchable by legitimate trading partners.

Though unrefined, a few of the mechanisms were able to adequately obfuscate the data. The overall opinion of the team was that this is a critical link to the future success of blockchain. The team also agreed that blockchain platforms, developers and cryptographers are now developing effective mechanisms that can provide efficient methods to protect sensitive data from prying eyes and to search for and share data among trading partners.

Data storage limitations:

As ledgers of transactions, blockchain platforms are not currently designed to efficiently store, index and retrieve vast amounts of data. This challenge is worked around in some blockchain applications by using near-block data storage solutions such as IPFS[13], Oraclize[14], IOTA[15], BigchainDB[16] and other services.

Also, some blockchain platforms are addressing the storage issue by incorporating data storage services or forming connectivity with existing data storage platforms (*ie.: Ethereum and IFPS*).

[11] When encrypting, you use **the reader's public key** to write message and the reader uses **their private key** to read it.
[12] When signing, you use **your private key** to write message's signature, and the reader uses **your public key** to check if it's really yours.
[13] IPFS: Interplanetary File System, a protocol and network designed to create a method of storing and sharing hypermedia in a distributed file system., https://ipfs.io/
[14] Oraclize: data-transport-layer for blockchain. www.oraclize.it/
[15] IOTA: designed to be the data layer for the internet of things. https://www.iota.org/
[16] BigchainDB: Database with blockchain characteristics, https://www.bigchaindb.com/

Multiple platforms:

Several blockchain platforms are currently in use and under development. They are being created as solutions in both the public domain and as in the private sector. As it is doubtful that one single platform solution will eventually be used across all industries, a key challenge is how the blockchain ledger concept and its programmability can be extended across platforms.

Many organizations are actively exploring ways for blockchain platforms to interoperate.

Cost:

Funding an industry-wide platform is a daunting challenge at best. However, there are many ways to fund such a solution including fees for memberships, volume-based subscriptions and transactions.

Costs fall into three categories:

1. Cost of building, deploying, maintaining and supporting the shared blockchain infrastructure
2. Cost of building, deploying, maintaining and supporting company-unique infrastructure *(e.g., local repositories including access control and help desks as well as adapters to feed the shared infrastructure)*
3. Cost of inefficiency *(incurred by trading partners trying to access local repositories and needed to recall username/password or work with the help desk of the repository owner)*

Many blockchain platforms have a built-in mechanism for supporting the transaction fee model to pay for the processing, connectivity and necessary data storage. Blockchain platforms use an electronic token or currency required for each transaction to fund the organizations that support the network.

Posting a transaction on a blockchain requires a fee for each process executed. Fees are paid from the account of the user much like how *E-Z*Pass deducts a fee every time you drive over a toll bridge. This provides an automated incentive for those companies supporting the operation of the platform and reduces processing fees for the companies that use the platform.

A volume-based subscription fee model could support pricing tiers based on volume. Firms would pay a fixed-price per month, based on their annual volume tier. The advantage of this model is that by offering fixed pricing, it makes it easier for firms to budget.

An underlying transaction fee or token model could be used by service providers to share fees based on usage. The automated models that are native to many blockchain platforms may be a bit of a culture change for corporations that are used to more traditional payment models.

ReferenceModels: **DSCSA and Blockchain**

Simulating the environment

A simulated environment allows teams to go beyond diagrams and to test certain hypotheses. Simulation is akin to building a prototype of real world and computerized systems and sheds insight into potential business changes by animating process, information and cash flows. It provides a virtual view into how regulatory interpretation and company policy affect trading partner behavior and helps to uncover details that may be overlooked when using diagrams alone to assess impact of change on a business environment.

Several scenarios discussed by the team were simulated throughout the course of the Study. The results of those simulations and the data they generated – referred to as ReferenceModels™ – were then shared and verified with the team.

The ReferenceModels depict existing processes in the supply chain and allowed the team to experiment with various strategies for using blockchain technology to support DSCSA requirements. After experimenting with many strategies, we settled on three (3) main ReferenceModels that incorporated different strategies for using blockchain technology to share, archive and evaluate the DSCSA Transaction Information (TI). Each model contains unique characteristics that affect the manner of sharing and the type of processing that each trading partner is responsible for to support the model.

The three models are:

- ReferenceModel™ 1

  Store full TI in an industry-shared blockchain platform for retrieval. Also, transact EPCIS events directly between trading partners to communicate the contents of shipments and logistics units.

- ReferenceModel™ 2

  Store addresses or pointers to trading partner portals or repositories of TI for retrieval in an industry-shared blockchain platform. Also, transact EPCIS events directly between trading partners to communicate the contents of shipments and logistics units.

- ReferenceModel™ 3

  Send DSCSA TI to blockchain platform distributed applications (DApps) that evaluate the data and store current "states" of the individual Product identifier. An expanded version includes shipment hierarchy and may alleviate the need to transact EPCIS events directly between trading partners.

A note on the ReferenceModels:

This was an exploratory Study. The ReferenceModels were used to provide some level of analysis of the outcome of Study team hypothesis. The ReferenceModels and all associated process flow and data model diagrams should be viewed in context of experimentation and not as finished, implementable artifacts. Some experiments continued until the team gained a specific insight and were not worked through to completion. Even though the data models use Entity Relationship Diagram notation, the relationships between data sets are for illustration purposes only. For instance, all models include data that is extracted from EPCIS events. The relationship between the Product Master dataset and the ObserveEvent dataset is an example of a suggested relationship. It is meant to suggest that the ProductID (in the form of a GTIN) in the Product Master dataset can be found in the EPC List of SGTINs in the EPC List. This relationship cannot be directly deployed in a database and only suggests that there is in fact, a relationship.

Establishing the Study framework

To aid in the exploration, the team established a framework (*see* ***Figure 3***) for discussing and understanding the interrelationships between the supply chain participants (supply chain sub-model), services (services sub-model) that may provide access to the blockchain and provide access to off-blockchain data, the blockchain and distributed network (data persistence sub-model) and the governance body (governance sub-model) which might be the gatekeeper to a private, permissioned blockchain platform, determine consensus data access rules and oversee the management of the system.

Core to keeping a clear distinction between what is necessary for DSCSA compliance, supply chain operations and potential trading partner to trading partner agreements, the team adopted three categories of design rules:

1. **DSCSA:** The rule can be directly linked to language in the DSCSA
2. **Supply Chain:** The rule exists due to established practices and trading partner needs
3. **Trading Partner Agreements:** Recognizing that trading partners can choose to share additional data based on their individual business arrangements

Defining these rules (categories) allowed the team to have targeted, exploratory discussions on several topics without blurring the lines between what is specifically called for in the law and what may be desired or needed by trading partners. Additionally, they helped in establishing ReferenceModel runs that tested whether data created in a trading partner to trading partner agreement can successfully be held confidentially in the shared industry blockchain.

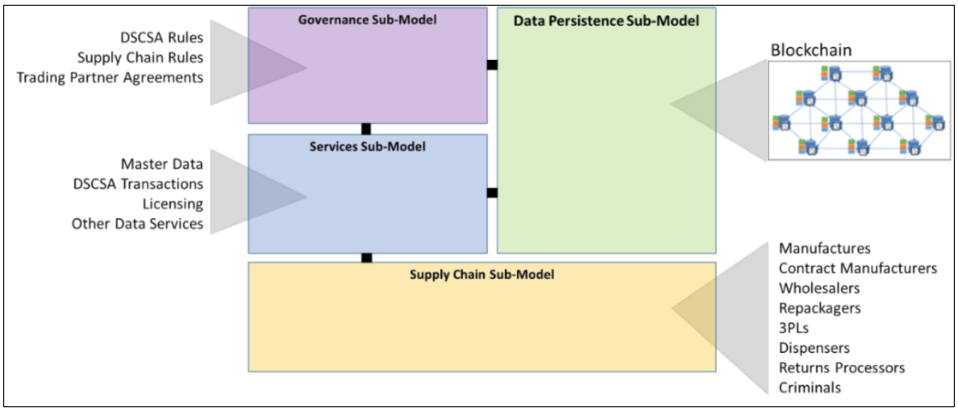

Figure 3:
Framework for Exploring Complexities

Although the team explored many avenues for using blockchain technology to support DSCSA requirements, we defined three models as alternatives. There were many variations within each model to accommodate different interpretations of the statute, governance issues, trading partner requirements and blockchain platform differences. The three ReferenceModels described here represent the major design alternatives that the team explored along with commentary from the team on their assessment of the models. We do not claim that they exhaustively represent the full range of possible solutions.

ReferenceModel 1:
Transaction Information Ledger

Definition

As shown in Figure 4, this model specifies that the data attributes of the DSCSA defined Transaction Information (TI) and Transaction Statement (TS) be stored in or, adjacent but accessible, to the blockchain platform. The initial version of this model specified that the TI attributes be stored in a blockchain transaction in an obfuscated manner. Currently, blockchain platforms are not designed to efficiently store, encrypt and retrieve large amounts of data. Most blockchain platforms extract a premium for storing data over a set limit. Encrypting and otherwise masking data must be accomplished prior to posting the data on the blockchain.

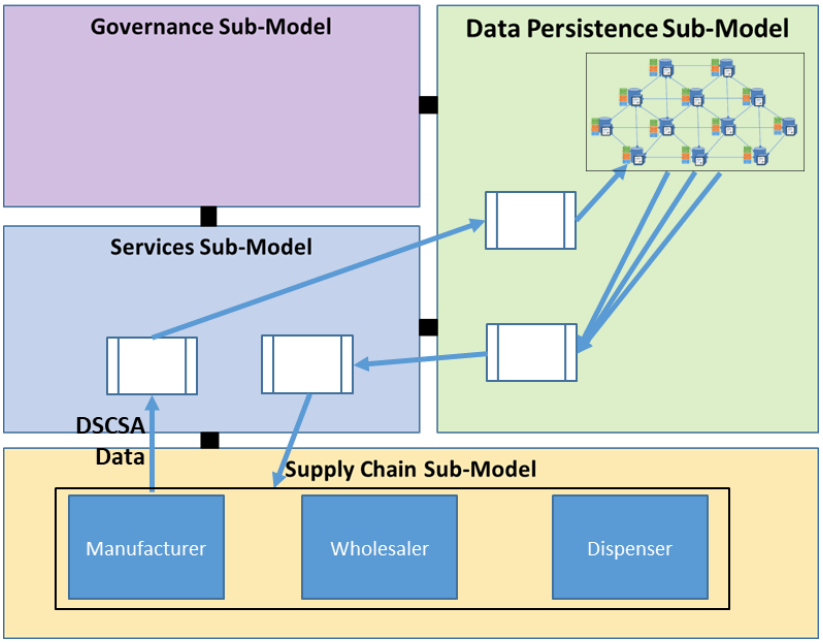

Figure 4:
ReferenceModel 1 – *TI/TS on the blockchain*

In ReferenceModel 1 (**Figure 4**), supply chain trading partners provide TI data to a service provider via a specified subset of GS1 EPCIS events. The provider (*provides access to the blockchain*) extracts essential data attributes from the EPCIS event and calls a distributed application (DApp), or other programs, on the blockchain platform established to process the event type.

The DApp checks to see if this trading partner is permissioned to post the type of event and if so, posts the event to the blockchain ledger. When event data are required, the trading partner sends an EPCIS Query Event to their service provider. The service provider's system calls the appropriate query DApp on the blockchain, which checks whether the trading partner has permission to the data. If so, the blockchain DApp retrieves the data and sends the data to the service provider who formats the data into an EPCIS Query response and sends it to the trading partner.

Assumptions

- Private, permissioned blockchain[17]
- GS1 Identifiers used for products, logistics units and parties
- Data on blockchain is encrypted or hashed
- Use of on blockchain programming (distributed applications, or DApps) to control posting and querying
- URI format of identifiers is used (SGTIN, GLN, SSCC, etc.)
- Use of EPCIS Event and Query data
- Use of EPCIS EventID to reference events
- Use of EPCIS standard "ErrorDeclaration" to indicate that an event identified by the EventID is voided
- Correcting Events must be posted for events declared in error

Feature observations

Governance:

As all DSCSA data is stored on the blockchain, it is most likely that the effort of governance will be high. All supply chain stakeholders posting data will, most likely, want representation during data visibility rule making (who gets to see what, under what circumstances). Implementation of the rules and validation of the programming code will also be complex.

Operations:

Each supply chain stakeholder (or their proxy) will be responsible for retrieving EPCIS Event data sets and evaluating them to make their own determination of actions. Evaluating data sets for each item under control (pallets, cases, totes, units) can cost resources and time.

Risk:

As each stakeholder evaluates the data available to them separately, this could lead to trading partners arriving at different conclusions about compliance. *For example, trading partners have their own policies as to whether a receiving event is necessary in acknowledgement of a shipping event*[18].

Cost:

High governance and operational costs.

Compliance:

Letter of DSCSA Law:

- *SEC. 203(g)(1)(A): "The transaction information and the transaction statements as required under this section shall be exchanged "*
- *SEC. 203(g)(1)(E): "facilitate gathering the information necessary to produce the transaction information for each transaction going back to the manufacturer"*
- ReferenceModel 1A fulfills letter of the law in that it includes all DSCSA data in one post and is accessible for retrieval

[17] Private, permissioned blockchain platforms allow industries to choose high performing network nodes and set and enforce criteria or rules for companies to access the blockchain.

[18] Relates to the use of GS1 EPCIS events and not blockchain itself.

- ReferenceModel 1B recognizes that trading partners exchange product master data and party master data prior to an order being executed (current best practice). This model assumes the trading partners already are in possession of product, customer and supplier master data and doesn't include it on the blockchain.

Intent of DSCSA Law:

ReferenceModel 1A and 1B could be regarded as both meeting the intent of the law. 1B provides additional efficiencies by adhering to master data management best practices.

Supply chain integrity:

Counterfeits:

As all DSCSA data is on the blockchain, it is possible to detect both a fake SNI and a fraudulent second commissioning of a legitimate SNI. Evaluation of packing and shipping events could detect duplication of an item.

Theft and reentry:

ReferenceModel 1 allows for "Recall" events to be posted. It may be possible to alert holders of items identified in a Recall event.

Exception management:

EPCIS contains an "Error Declaration" element that can be used to indicate that an EPCIS event is in error and identify the replacing event.

SWOT analysis:

Strengths:

1. Simple design complies with DSCSA requirements
2. DSCSA TI data is kept together as a record of truth at a specific point in time. Changes to trading partner and product information do not affect the data recorded at the time of the blockchain transaction.

Weaknesses:

1. Obfuscating data and making it accessible and interpretable by the correct parties is an issue with this and all models.
2. Currently, data must be obfuscated prior to posting to the blockchain, making it difficult to look up needed data. A mechanism outside of the blockchain must be used to share keys and indicate which transaction applies to each shipment which re-introduces the requirement of establishing an electronic connection with many trading partners (*a main reason for blockchain exploration*).

   A possible alternative might be to assign a set of identities with random addresses (like randomized serial numbers), making it hard to correlate all the different packages that a trading partner is shipping. But, the information does not require decrypting. Instead, some control node (possibly controlled by the trading partner) can correlate the source of the packages when needed. This is like a manufacturer maintaining a list of commissioned serialized packages.

3. Massively duplicated product and party master data (data about the product, supplier or customer). Product and party master data are typically acquired prior to an order. As the DSCSA includes a 2023 requirement[19] to gather previous TI information, this means that data either needs to be stored at the DSCSA defined package level (package level granularity), or via sophisticated algorithms to trace back through the various logistic units, a package has been part of in its lifetime.

   In the case of package level granularity, product and party master data would be duplicated for each package produced. This would increase data storage requirements, cost and risk of data errors.

Opportunities:

1. If obfuscation and on-block data storage challenges are resolved, the TI information could be normalized[20] and stored efficiently on a blockchain (*see ReferenceModel 3 below*).
2. There are "add on" services that can augment blockchain storage or provide blockchain benefits in a platform that can also manage large quantities of data efficiently (ie: BigchainDB, IPFS, etc.). These services can provide a link in the blockchain transaction to the actual data. Groups are actively working on integrating storage capacity services that can meet the industry's performance needs.
3. Private, permissioned blockchains can be configured to accommodate data sets relatively economically due to the option of specifying performance metric meeting network nodes.
4. Links to off-block sources or the use of blockchain oracle technology could be added to expand the use of this data beyond DSCSA compliance.

Threats:

1. Obfuscating billons of blockchain transactions could result in a large "key management" issue for trading partners. Managing keys may be a larger challenge than managing the DSCSA data itself for small trading partners.
2. Loss of keys could disrupt product flow while key exchange is established manually.

Observations:

1. Posting the entire TI on the blockchain as one large transaction rather than posting it in logical groupings makes the data more difficult to use for purposes other than DSCSA compliance. Product and Party master data should not be repeated for each transaction. The idea of normalizing the data and posting data groups in separate transactions would mimic how data is stored in databases and could be used or expanded for other purposes. *ReferenceModel 3 expands on this concept.*
2. Because TI data is committed directly to the blockchain and data access rules are established and enforced by DApps, data governance becomes a complicated and costly burden. All companies posting data will want representation when the access rules are established, implemented and verified. This model would enact a large data governance commitment in terms of resources and cost on trading partners.

[19] See "Traceability Requirement" in Appendix. Note: Some parties do not make this same interpretation of the statute. It was used, however, for the purposes of this Study.

[20] Normalization is a process to group like data attributes together, minimizing duplication.

ReferenceModel 1:

Life cycle of a pharmaceutical package

Posting data to the blockchain

Here is an example of the use of ReferenceModel 1 (see Figure 5), where GS1 EPCIS event data is stored directly on the blockchain:

Prior to transacting, the trading partners (*manufacturer, wholesaler and dispenser*) would exchange their blockchain Account ID and possibly public keys (to decrypt posted transactions). A manufacturer would create and hold EPCIS events as product is labeled, packed into cases, cases packed onto pallets and shipped to the purchasing wholesaler. Upon shipping the product to the wholesaler, the manufacturer would post the held EPCIS events (commissioning, packing and shipping) to the blockchain for the packages, cases and pallets shipped. The wholesaler would be alerted to this shipment by one of three possible avenues:

1. An Advanced Shipment Notice
2. Direct EPCIS XML event delivery
3. Alert from a DApp on the blockchain via their blockchain Account ID

The wholesaler would either evaluate the directly delivered EPCIS events (and possibly match them with the blockchain posted data) or retrieve the blockchain posted data and treat it as the one source of truth. This process would be repeated for the transaction between the wholesaler and dispenser as depicted in **Figure 5**.

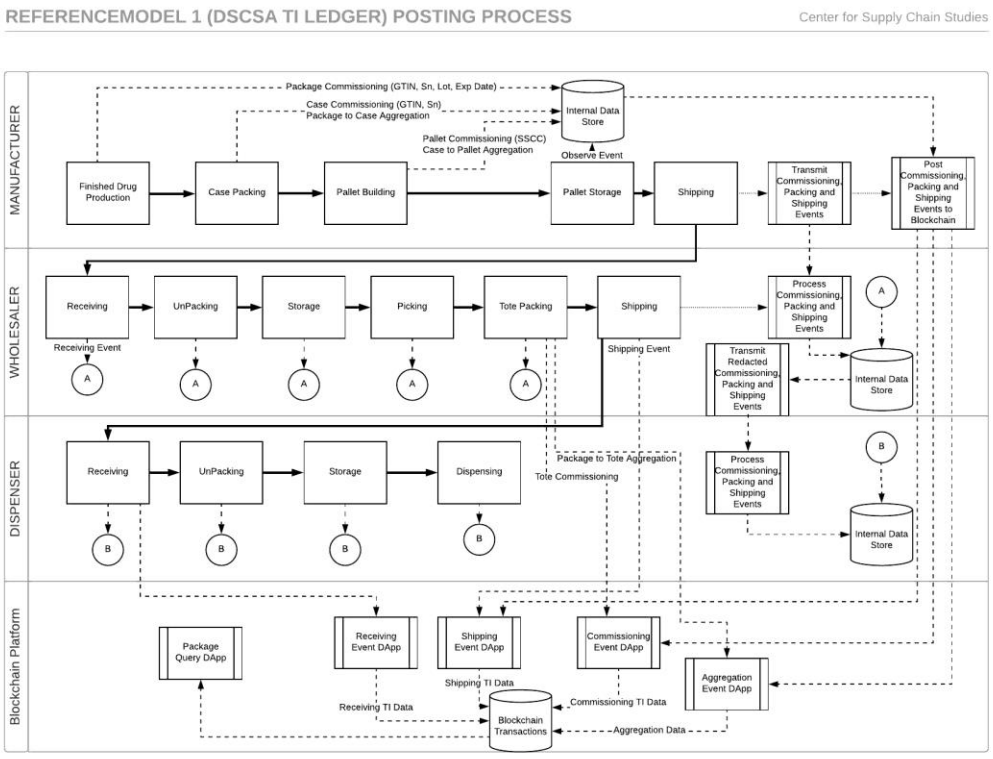

Figure 5:
ReferenceModel 1 – *DSCSA TI data on the blockchain*

ReferenceModel 1:

Verifying the manufacturer place a package into commerce

For any trading partner to verify that a package was placed into commerce, they would need to access the commissioning data that the manufacturer posted or shared. If the commissioning data was shared directly via an GS1 EPCIS commissioning event, the trading partner would know that it was placed in commerce. What they *wouldn't* know is whether anything occurred in the interim that would cause them to not sell, transfer, dispense or administer the product.

Using ReferenceModel 1, the trading partner could query the blockchain to retrieve all transactions they were legitimately allowed (data governance rules) to access. The trading partner would be able to assess whether the manufacturer, or anyone else in the supply chain had posted an event that would render the product unusable (recall, damage, expired, etc.). **Figure 6** diagrams the verification process for the sample wholesaler and dispenser.

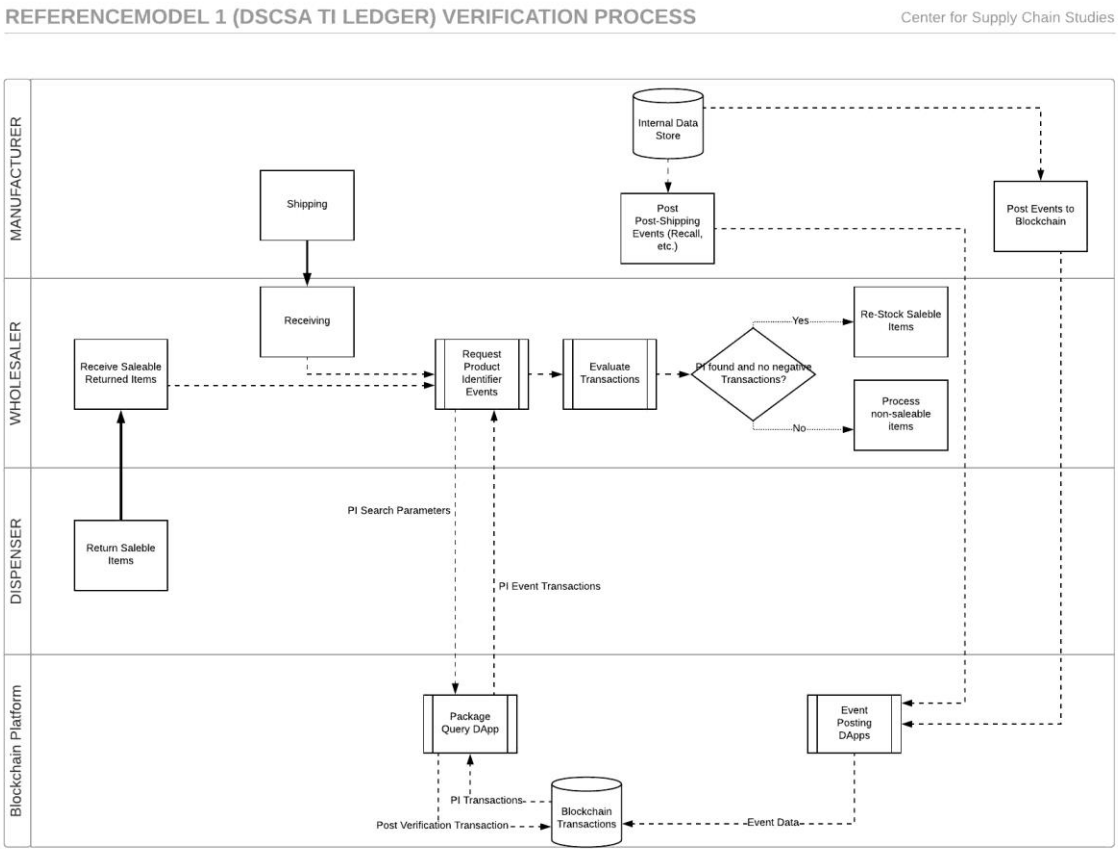

Figure 6:
ReferenceModel 1 – *Verification Process*

ReferenceModel 1:
The Data

The data depicted in **Figure 7** is non-normative and was used to experiment with placing the TI data on the blockchain. It shows the data that each trading partner holds internally and the data that is posted to the blockchain platform.

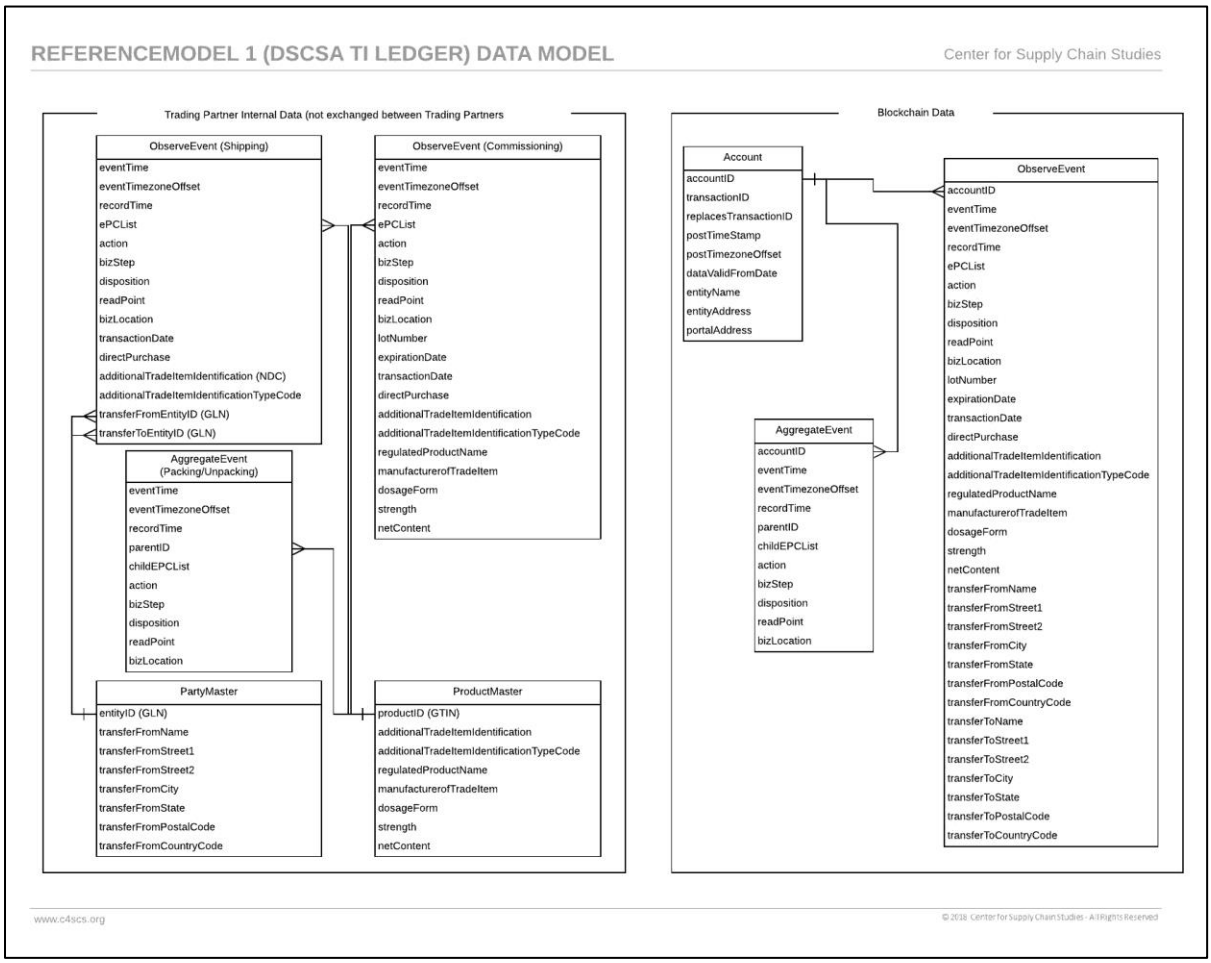

Figure 7:
ReferenceModel 1 – *Trading Partner and Blockchain Data*

ReferenceModel 2:
Directory service

Definition

As shown in **Figure 8**, this model specifies that pointers, or addresses to EPCIS repositories, DSCSA portals or other services be stored in the blockchain. The blockchain would serve as a sort of "directory" of DSCSA and other data. Hash values calculated on original EPCIS events are also posted to the blockchain along with the repository address and can be used later to determine if the retrieved data matches the original data provided by the authoring trading partner.

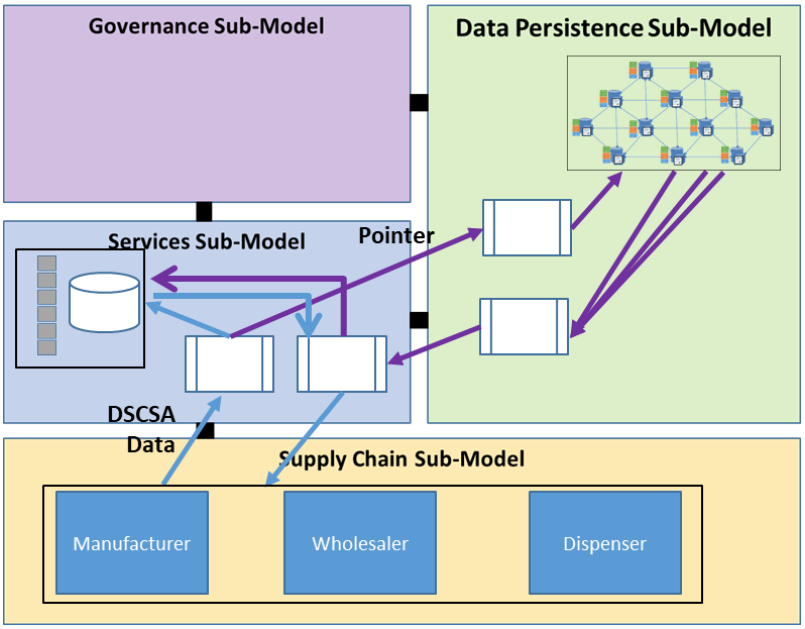

Figure 8:
ReferenceModel 2 – *Directory Service*

In ReferenceModel 2, supply chain trading partners provide TI data to a service provider via GS1 EPCIS events. The service provider stores the events in a repository and calculates a hash value based on the event. The service provider calls a DApp on the blockchain platform established to process the event type. The call includes the hash value and the address established by the service provider where EPCIS queries are accepted and processed. The DApp checks to see if this trading partner is permissioned to post the information and if so, posts information to the blockchain ledger.

When event data are required, the trading partner sends an EPCIS Query Event to their service provider. The service provider's system calls the appropriate query DApp on the blockchain, which checks whether the trading partner has permission to the data. If so, the blockchain DApp retrieves the hash and address of the service provider holding the original event. The trading partner's service provider then queries the data source address and retrieves the EPCIS event data. The hash value can then be checked to ensure the retrieved event data is identical to the event sent by the original trading partner. The service provider then provides the event data to the querying trading partner.

Assumptions

1. Private, permissioned blockchain[21]
2. GS1 Identifiers used for products, logistics units and parties
3. Data on blockchain is encrypted or hashed
4. Use of on blockchain, programming (distributed applications, or DApps) to control posting and querying
5. URN and URI formats of identifiers (SGTIN, GLN, SSCC, etc.) are used
6. Use of EPCIS Event and Query data
7. Use of EPCIS EventID to reference events
8. Use of EPCIS standard "ErrorDeclaration" to indicate that an Event identified by the EventID is voided
9. Correcting Events must be posted for events declared in error

Feature observations

Governance:

As all DSCSA data is stored off the blockchain in private repositories controlled by the supply chain stakeholder or their solution provider. It is most likely that the effort of governance will be low in terms of data access of blockchain data.

Each EPCIS Repository establishes and executes their own data governance rules. There is the potential for disputes if querying parties and queried parties disagree on whether events should be shared or if data elements should be redacted. Implementation of the rules and validation of the programming code will also be complex on an individual EPCIS Repository basis. However, the bulk of governance activity will be in defining standardized data access protocols for individual EPCIS repositories:

1. Standards will need to be developed with which trading partners will need to comply to make their data accessible. This is likely to be a similar effort to defining data standards for keeping all data on the blockchain.
2. Governance will be needed to enforce the standard when a query to a trading partner fails.

In comparing ReferenceModel 1 and 2, the issue shifts from relying on third-party solution providers to preserve the confidentiality of the data on the blockchain to relying on each supply chain partner to control their own data. This will likely require more "governance" and more cost, but it may make executives feel more comfortable with the security of their confidential data.

Operations:

Retrieving EPCIS Event data is a two-step process in ReferenceModel 2.

First the querying party must retrieve the EPCIS Repository address for the object in question, then retrieve the DSCSA data from the addressed EPCIS Repository. This process may repeat itself as it is possible that certain events (Shipping, Receiving) may be accomplished at the outer packing hierarchy level. In that case, the querying party may need to apply an algorithm or series of queries to navigate the packaging hierarchy.

Each supply chain stakeholder (or their proxy) will be responsible for retrieving EPCIS Event data sets and evaluating them to make their own determination of actions. Evaluating data sets for each item under control (pallets, cases, totes, units) can cost resources and time.

[21] Private, permissioned blockchain platforms allow industries to choose high performing network nodes and set and enforce criteria or rules for companies to access the blockchain.

This system also requires that each local repository be available 24x7 to respond to queries that can occur on a 24x7 basis because significant elements of the supply chain operate around the clock. Each repository would then need to provide solution to maintain uptime through both scheduled and unscheduled (emergency) maintenance activities.

Risk:

As each stakeholder evaluates the data available to them separately, there could be issues of trading partners arrive at different conclusions (regarding compliance). Each individual EPCIS Repository may have different response times for returning query results.

Cost:

Lower Governance cost for data stored on the blockchain, however, higher cost in managing data locally and responding to trading partner's queries. Also, due to the added number of processing steps, there may be a higher cost to retrieve data than ReferenceModel 1.

Trading partners will also have to develop governance processes from establishing access control accounts for third-party access to their repositories, as well as help desks to support third parties legitimately accessing data in the repositories.

With a multiplicity of repositories to access – each of which may have difference procedures – trading partners will incur costs in time lost gaining access to repositories and using trading-partner help desks to help them "remember" each company's procedures and logon credentials.

Compliance:

Letter of DSCSA Law:

ReferenceModel 2 fulfills letter of the law in that it includes all DSCSA data in one post available in the queried EPCIS Repositories.

Intent of DSCSA Law:

ReferenceModel 2 could be regarded as meeting the intent of the law, however, there may be difficulty in determining duplicate SNIs.

Supply chain integrity:

Counterfeits:

The Industry blockchain will hold multiple addresses for each item (manufacturer, wholesaler, dispenser, etc.). Only by querying and retrieving DSCSA data from all addresses can an evaluation be made whether there is a single trail back to the manufacturer or multiple. It's not clear what stakeholder might take on that responsibility.

Recalls:

ReferenceModel 2 allows for "Recall" events to be posted. In a pure "repository address only" model, a Recall event would look like any other event unless the EPCIS Repository was queried. An additional mechanism or indicator may be needed on the industry blockchain to more quickly identify recalled items and alert holders of those products.

Exception management:

EPCIS contains an "Error Declaration" element that can be used to indicate that a EPCIS Event is in error and to identify the replacing event.

SWOT analysis:

Strengths:

Data control is guaranteed in that data is held directly by the authoring trading partner or their proxy service provider. Each trading partner can implement their own set of data access requirements and rules.

Weaknesses:

1. Obfuscating data and making it accessible and interpretable by the correct parties is an issue with this and all models.
2. Because TI data is stored in separate repositories, DApps may not be able to detect duplicate PI data. Duplicate PI data may occur because of a data or processing or labeling error or because of counterfeit activity.
3. The number of interfaces and transactions necessary to post to the blockchain and retrieve data is far greater than the other models.
4. For the system to work, there needs to be conformance to norms and performance metrics to keep the solution from becoming needlessly complex and costly.
5. The possibility that a repository is down at a time when it is needed is high, given the large number of repositories required and the high cost of providing 24x7 uptime.
6. Each trading partner would need to manage access control for its repository. This would likely also require providing help-desk service to resolve issues when other trading partners encounter issues accessing the repository.
7. Trading partners seeking to lookup data may have to manage many accounts IDs and passwords to access the various repositories. And because such accesses may be infrequent, outside partners would not memorize the unique access information for each trading-partner repository. They would likely require help-desk support on an ongoing basis.
8. If encryption keys are used to protect the data in a repository, key management may be complex and costly.

Opportunities:

This model can be extended to include links to additional data stores that may valuable for other trading partner processes.

Threats:

Because of the complexity of managing access for hundreds of repositories, there is a high likelihood that some repositories would be vulnerable to attack to gain access to their contents. This could be for reasons of competitive intelligence or more nefarious purposes.

Observations:

The current model is based on a single directory. It may be the case that the directory concept would be implemented in different blockchains. In this case, an additional layer of interoperability between directories would be needed. Interoperating across directories could impact performance, add data governance complexity and add cost or add complexity to service calculations.

ReferenceModel 2:
Life cycle of a pharmaceutical package

Posting data to the blockchain

As an example of the use of ReferenceModel 2, where addresses where GS1 EPCIS event data could be accessed is stored directly on the blockchain. The hash value of the EPCIS event data would also be posted on the blockchain to act as a check once the actual data was retrieved from the trading partner.

Prior to transacting, the trading partners (manufacturer, wholesaler and dispenser) would exchange their blockchain Account ID and possibly public keys (to decrypt posted transactions). A manufacturer would collect EPCIS events as product is labeled, packed into cases, cases packed onto pallets and shipped to the purchasing wholesaler. Upon shipping the product to the wholesaler, the manufacturer would post the address of their EPCIS repository (held by them or their solution provider) along with the hash of each EPCIS event data set. The wholesaler would be alerted to this shipment by one of three possible avenues:

1. An Advanced Shipment Notice
2. Direct EPCIS XML event delivery
3. Alert from a DApp on the blockchain via their blockchain Account ID

In the scenario where the wholesaler did *not* receive the EPCIS event directly, they would query the blockchain for the addresses where EPCIS repositories holding events for the package in question. The wholesaler's system would then query each EPCIS repository and retrieve the available events. The wholesaler would then calculate a hash value for the events and match against the blockchain version of the hash value. Upon matching, the retrieved EPCIS events would be treated as the one source of truth. This process would be repeated for the transaction between the wholesaler and dispenser (depicted in **Figure 9**).

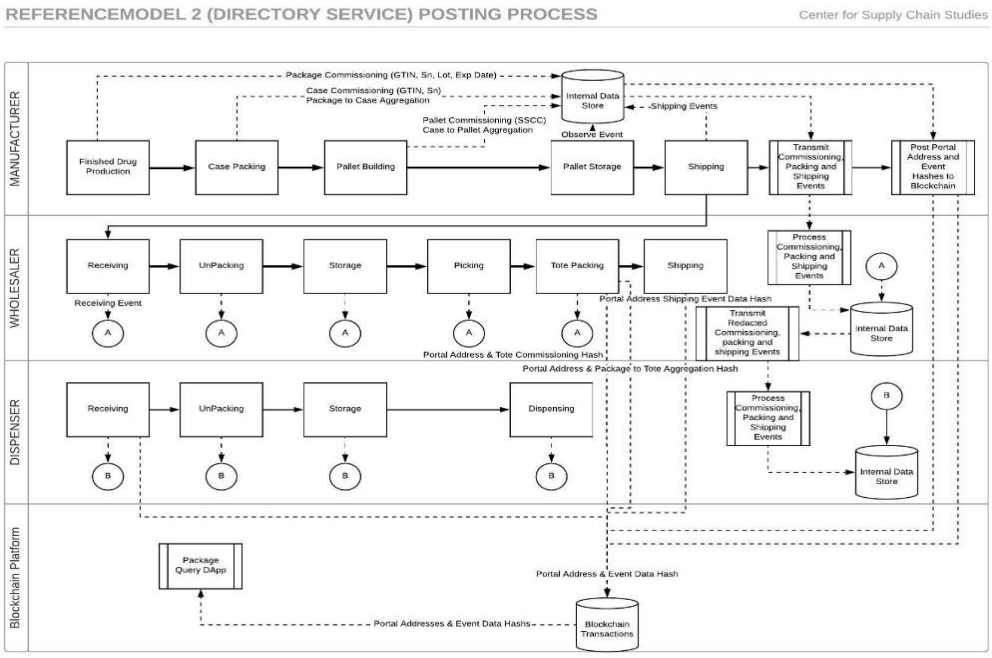

Figure 9:
ReferenceModel 2 – *Directory Service*

Verifying the manufacturer placed a package into commerce

For any trading partner to verify that a package was placed into commerce, they would need to access the commissioning data that the manufacturer holds. The trading partner would repeat the process outlined above of first retrieving the EPCIS repository addresses from the blockchain and then querying those addresses for the commissioning data. The trading partner would know that it was placed in commerce. However, they would *not* know whether anything occurred in the interim that would cause them to not sell, transfer, dispense or administer the product.

This process might be supplemented by a separate "verification" database maintained by the manufacturer to explicitly support verification lookups. But, each manufacturer then would be responsible for ensuring that the query came from someone owning the package in question.

Using ReferenceModel 2, the trading partner could query the blockchain to retrieve all transactions they were legitimately allowed (data governance rules) to access. The trading partner would retrieve those events and evaluate them to determine whether the manufacturer, or anyone else in the supply chain had posted an event that would render the product unusable (recall, damage, expired, etc.). Figure 10 diagrams the verification process for the sample wholesaler and dispenser. (*See **Figure 10**.)*

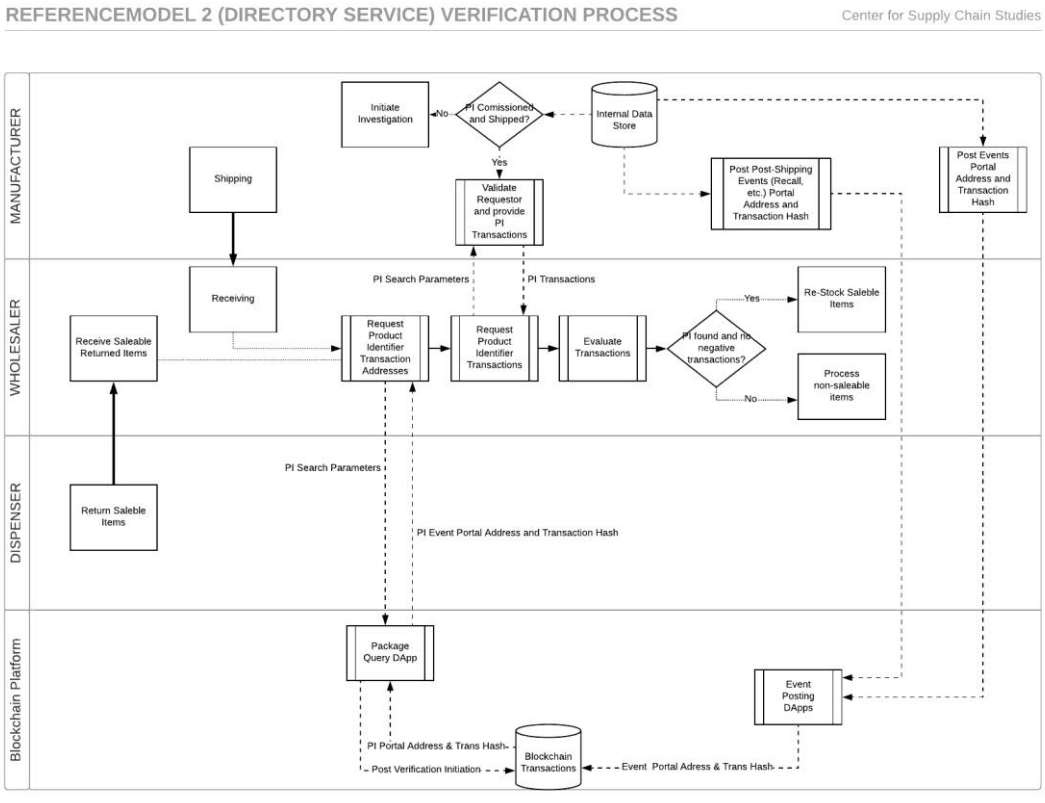

Figure 10:
ReferenceModel™ 2 – *Directory Service Verification*

ReferenceModel 2:
The Data

The data depicted in **Figure 11** is non-normative and was used to experiment with placing the TI data on the blockchain. It shows the data that each trading partner holds internally and the data that is posted to the blockchain platform.

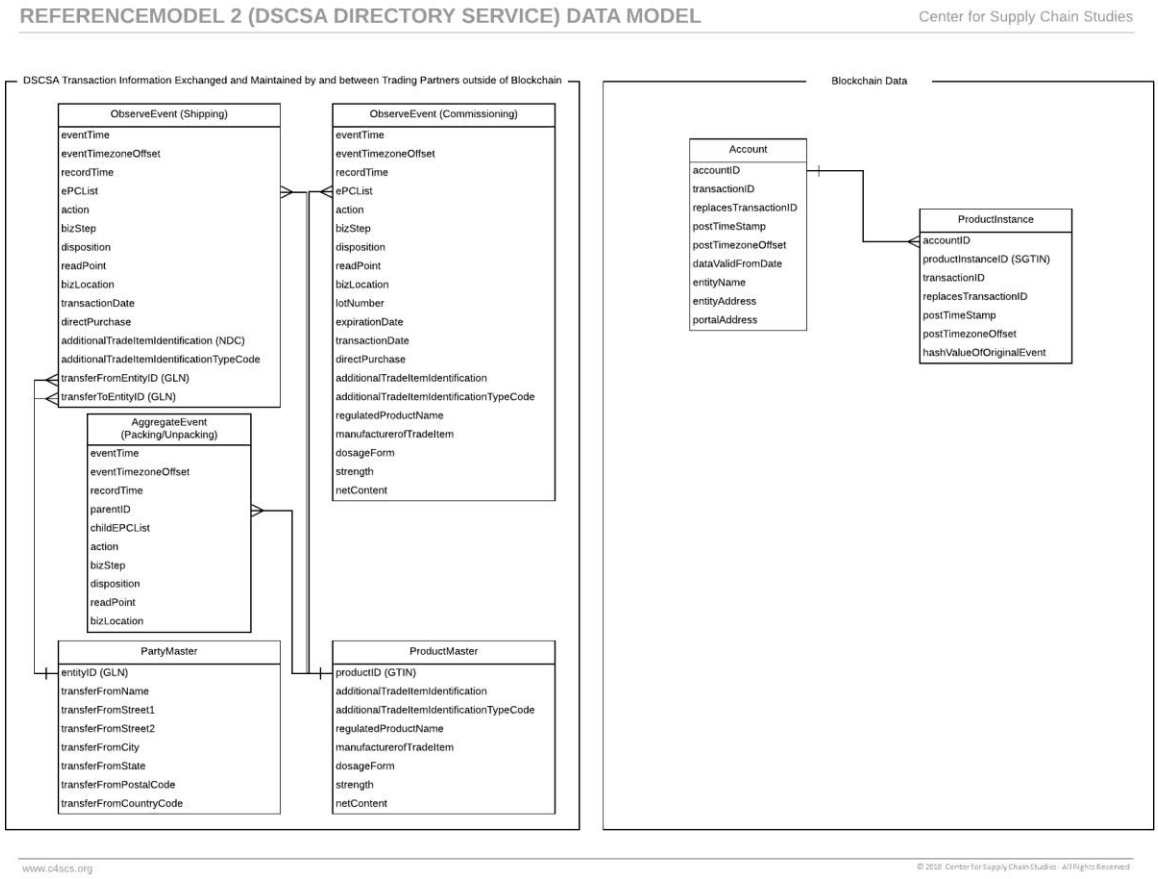

Figure 11:
ReferenceModel 2 – *Trading Partner and Blockchain Data*

ReferenceModel 3:
Product "states"

Definition

This model takes a different approach to DSCSA and operational requirements than in ReferenceModels 1 and 2. Although this model calls for the archival of EPCIS events (for investigation purposes), it only stores a few "states" of the package as it transitions the supply chain. The model relies on *on-blockchain* DApps to interpret incoming EPCIS events, archive them and post only the "state" of the package. The premise is, if DApp code is visible to all, then all can validate that the code would interpret a given set of incoming data (or EPCIS event) and all could trust the "state" that the DApp set based on the incoming data and visible DApp logic. The "states" constitute actionable information, upon which trading partners could make predictable business decisions. *The States we explored were:*

1. **DSCSA product:** ***Does the product fall under the DSCSA?*** Non-DSCSA items in the supply chain will be serialized. It is difficult for downstream trading partners to be aware of which products fall under DSCSA and which do not. This state could save resources in quarantining non-DSCSA product unnecessarily, believing it might be a DSCSA product without the required TI/TS.
2. **Grandfathered:** ***By Nov. 2018, all product that falls under the DSCSA will be serialized.*** However, passing serialized TI is not required until 2023. There will be a period after 2023 where there will exist serialized product without TI and serialized product with TI. The Grandfathered state identifies those products that legitimately do not have associated TI available. These products will all exit the supply chain at some point. At that point, this state will be unnecessary.
3. **Fit for Commerce:** There are many events that would indicate that a package was not fit for commerce (*such as recall, damage, expired product, temperature excursion, determination of illegitimacy, etc.*). If the posting DApp encounters any of these events, it posts a "fit for commerce" state of false. This gives a clear indication to supply chain and clinical operations as to what should be done with the product.
4. **In Commerce:** ***Has the product been placed in commerce by the DSCSA-defined manufacturer?*** This state provides some level of security in that it is not set to "true" until the manufacturer ships or places it into commerce. This state would provide a clear data point for wholesalers attempting to verify saleable returns and inspections involving counterfeit or stolen products.
5. **Provenance:** ***Have the observed transactions regarding a package added up to a clear link back to the manufacturer?*** If an investigation were to take place, would the archived transactions show the series of TI's back to the DSCSA defined manufacturer.
6. **Declared Emergency:** The DSCSA contains provisions where TI and TS sharing can be suspended in the event of a declared emergency. To not render that product illegitimate after an emergency, a manufacturer (*or entity that transferred the product*) must declare which product was part of the emergency. This state provides the mechanism to make that declaration clear to all trading partners that may receive the product in the future.
7. **Declared Emergency ID:** While not a "state," the team experimented with a way to identify the emergency and which authority declared it.

The team explored two alternatives to maintaining the state of the package on a blockchain. The first was to introduce an Internet of Things (IoT) concept by creating an address for each thing (*package*). This was accomplished by creating a DApp for each package using a hashed version of the PI as the name of the DApp (thereby creating a sort of address for each package). The states were maintained in the DApp's allocated memory.

Because DApp deployment on the blockchain is expensive, the second alternative involved exploring a method for posting transactions that list the latest state. While not as IoT-like as the DApp method, it did remove the burden for each subsequent trading partner to accurately evaluate a growing string of events. This method drastically reduced trading partner processing and risk that trading partners of theirs could interpret the events differently. This model also reduces the risk that regulators (FDA, State Boards of Pharmacy, etc.) could interpret a series of events differently than the trading partner.

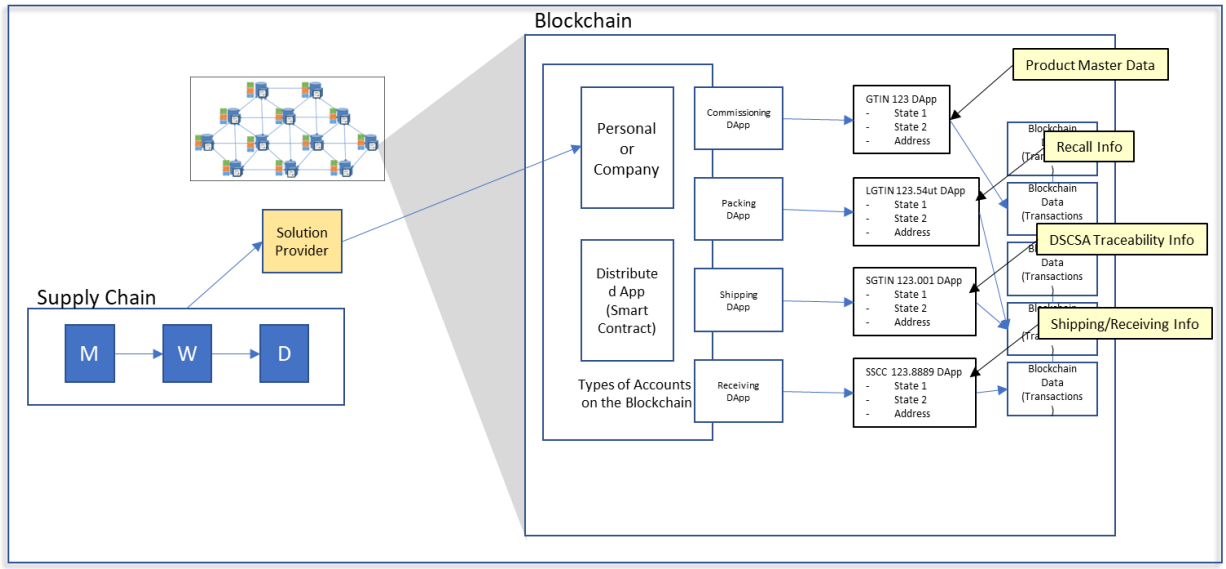

Figure 12:
ReferenceModel 3 – *Product, Lot, Package and Logistics Unit State*

Expanding the value of state management

Links for additional information:

While this model was designed to provide quick answers to pressing question of trading partners, there is also the need to link back to the EPCIS events that were evaluated by the DApps (to determine that state). Therefore, we explored adding a link attribute to the states which allowed for trading partners to retrieve associated events and for entities to provide additional data associated with the product that might be of value beyond DSCSA compliance.

Other "things":

As depicted in **Figure 12**, the concept of maintaining state and links to other information can be expanded to create efficiencies (less duplicate data) and added value for DSCSA and other needs. *They include:*

1. **Product Information:** Identified by a GS1 Global Trade Item Number (GTIN), information about products (master data) can be posted to cover minimum DSCSA needs and links to more, in depth data.
2. **Entity Information:** Trading partners in the models are identified by their GS1 Global Location Number (GLN). Master data about the entity or location can be accessed through a posted link.
3. **Product Lot:** Expiration Date and Lot number are set by the manufacturer for each Lot produced. This and other information about the Lot could be posted here. Recalls typically are at the Lot level. Recall events could set a state at the Lot level advising of the recall and setting a link for more information.
4. **Package:** This level of information has been covered in the basic description above. Each package could have a series of states to reflect the context of the package.
5. **Logistics Units:** Identified by the GS1 Serial Shipping Container Code (SSCC), this set of data could include packaging hierarchy, which is needed for receiving, inference and in the event of selling through sealed manufacturer cases, providing TI to trading partners.

The Transaction Information (TI) defined within the DSCSA law contains data attributes about many levels of product hierarchy and logistics units. Those levels can be identified using GS1 and other standards.

Table 1:
State can be maintained for products, instances, logistic units and locations

Object	Standard ID	Example[22]
Finished Product	GS1 GTIN	urn:epc:id:sgtin:0031234.500012.0
Finished Product Lot Info	GS1 LGTIN	urn:epc:id:lgtin:0031234.500012.201801ABC
Serialized Finished Product	GS1 SGTIN	urn:epc:id:sgtin:0031234.500012.12345
Logistics Unit	GS1 SSCC	urn:epc:id:sscc:0031234.500043.12345678
Entity	GS1 GLN	urn:epc:id:sgln:031234.500001.0
Location	GS1 GLN	urn:epc:id:sgtin:031234.500012.0
Internal Location	GS1 GLN + Extension	urn:epc:id:sgtin:031234.500012.12345
Document	GS1 GDTI	urn:epc:id:gdti:031234.000123.12345

[22] See GS1 Tag Data Standard for explanation of format: https://www.gs1.org/standards/epcrfid-epcis-id-keys/epc-rfid-tds/1-11

Assumptions

1. Private, permissioned blockchain[23]
2. GS1 Identifiers used for products, logistics units and parties
3. Data on blockchain is encrypted or hashed
4. Use of on blockchain programming (distributed applications, or DApps) to control posting and querying
5. URN and URI formats of identifiers (SGTIN, GLN, SSCC, etc.) are used
6. Use of EPCIS Event and Query data
7. Use of EPCIS EventID to reference events
8. Use of EPCIS standard "ErrorDeclaration" to indicate that an Event identified by the EventID is voided
9. Correcting Events must be posted for events declared in error

Feature observations

Governance:

All sensitive DSCSA data is stored off the blockchain in private repositories controlled by the supply chain stakeholder or their solution provider. Indicators based on industry consensus are stored on the Industry blockchain. It is most likely that the effort of governance will be much lower than ReferenceModel 1, as the states may prove to expose less confidential data and a bit higher than ReferenceModel 2. Consensus on the indicators may only be needed initially or upon addition of indicators.

Operations:

Retrieving actionable data is straightforward. The hash of the SGTIN or SSCC is the distributed application name. Supply chain partners obtain the SGTIN or SSCC of the outer packaging layer from the item's barcode. No evaluation of EPCIS event sets is necessary by individual trading partners. No dependency on individual EPCIS Repository latency.

Risk:

Low: The distributed application is verified and agreed by the industry and regulators. Validation of that code is provided to all. The executed code is visible to all. Low risk to industry stakeholders and regulators.

Cost:

The main governance activities are to form consensus on the rules and logic that would be used to determine the state of the package, as well as the actions to be taken if trading partners should be alerted if the state is incorrect for the incoming event. *For example*, a package with the state of "fit for commerce" is false and the incoming event is a forward logistics shipping event (*the trading partner is trying to ship a package that is not fit for commerce*).

[23] Private, permissioned blockchain platforms allow industries to choose high performing network nodes and set and enforce criteria or rules for companies to access the blockchain.

Compliance:

Letter of DSCSA Law:

ReferenceModel 3 fulfills letter of the law in that it includes addresses for the full DSCSA data set either in individual EPCIS Repositories, or Repositories accessible by blockchain programming.

Intent of DSCSA Law:

Duplicates not possible.

Supply chain integrity:

Counterfeits:

Each legitimately commissioned item will have one (*and only one*) entry. Duplicates are not possible. A manufacturer (or repackager) would be alerted immediately if another distributed application with the same identifier existed.

Theft and reentry:

ReferenceModel 3 allows for "Recall" and other events ("stolen") to be posted and reflected in the indicators (Fit for Use).

Exception management:

EPCIS contains an "ErrorDeclaration" element that can be used to indicate that a EPCIS Event is in error and to identify the replacing event. The programming would reverse the previous indicator settings and apply the new ones.

Note: Reconfiguring the indicators may create an issue for supply chain partners that have already processed the item. Future work in this area should explore whether these supply chain partners receive an alert to the changes and on what states an alert might be given.

SWOT analysis:

Strengths:

1. Provides actionable information to trading partners. Certain trading partners, processing high quantities with very short time limits may not have the luxury of time to evaluate a series of EPCIS events for each and evert package that move through their operation each night.
2. Provides one source of truth that can be trusted by trading partners and regulatory authorities.
3. Reduces the data load and processing time for trading partners.

Weaknesses

1. Obfuscating data and making it accessible and interpretable by the correct parties is an issue with this and all models.
2. Although Provenance is one of the states, there are issues with determining whether a clear set of TIs have been encountered (*trading partners using more than one entity identifier, non-participating trading partners*).
3. If encryption keys are used to protect the data in a repository, key management may be complex and costly.

Opportunities:

1. Could be expanded to provide many kinds of data to serve operational, clinical and contractional processes.
2. Provides one source to connect to other systems (Product Master Data, Temperature Monitoring, etc.).
3. As with ReferenceModel 1, this model can detect duplicate entries, representing legitimate, correctable errors, or potentially counterfeit product.

Threats:

The obfuscation mechanism (*using blockchain oracles*[24] *to interact with encrypt and decrypt data*) may provide a single point of attack.

Observations:

This model attempts to move from duplicating the history of separately evaluating transactions to determine actions to a consensus-based view of items in the supply chain. It could reduce the "re"-processes (*reorders, reshipping, reconciliation, reimbursements, etc.*).

[24] Specialized applications on the blockchain, provided as a service, to retrieve data that is not stored on the blockchain. For example, retrieving ambient temperature for a specific location from a trusted weather service.

ReferenceModel 3:

Life cycle of a pharmaceutical package

Posting data to the blockchain

As an example of the use of ReferenceModel 3 (*where states are determined by industry agreed DApps and minimal data about the product*), package, Lot and shipment are posted to the blockchain provide trading partners actionable information without having to individually evaluate a series of EPCIS events. Prior to transacting, trading partners (manufacturer, wholesaler, dispenser) would exchange their blockchain Account ID and possibly public keys (to decrypt posted transactions). The manufacturer would also post minimal product master data.

A manufacturer would create and hold EPCIS events as product is labeled, packed into cases, packed onto pallets and shipped to the purchasing wholesaler. Upon shipping the product to the wholesaler, the manufacturer would call a DApp, using the held EPCIS event dataset as parameters. The DApp evaluates the data and sets certain states and information for the Lot, package or shipment. The wholesaler would receive an alert that a shipment was posted and could then query the blockchain using the following (*may be masked or hashed*):

Table 2: *Query Parameters*

Query parameter (urn format)	Retrieves
GTIN (Global Trade Item Number)	Limited product master data required by DSCSA + Does product fall under the DSCSA statute.
SSCC (Serial Shipping Container Code)	Hierarchy of the shipment (pallet, cases, packages). Used for receiving.
LGTIN (Lot Global Trade Item Number)	Lot level information: Lot #, Expiration Date, Recall State of the Lot, Is Lot Grandfathered?
SGTIN (Serialized Global Trade Item Number)	Package SGTIN placed in commerce? Fit for Commerce (*no events such as recall, damage or expiration*)? Provenance exists? Declared emergency (may not have DSCSA TI data because it participated in shipments during a declared emergency).

This process would be repeated for the transaction between the wholesaler and dispenser as depicted in **Figure 13**.

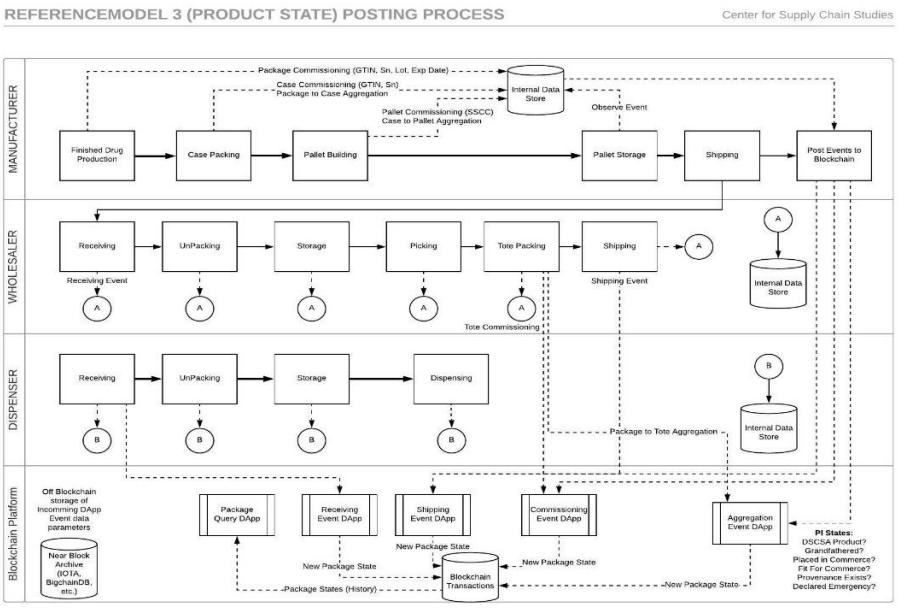

Figure 13:
ReferenceModel 3 – *Posting to the Blockchain*

Verifying that manufacturer placed a package into commerce

As the DApps have evaluated incoming EPCIS transactions according to industry agreement, the trading partner has enough information from the receiving process outlined above to determine whether a package was placed into commerce.

However, if the trading partner would like a second check (*incase additional events have caused the package's state to change*), the trading partner would query the blockchain using the URN format of the GTIN, LGTIN or SGTIN (most likely, the hashed value of the URN format with a unique seed value to keep the data confidential). The retrieved states will provide the trading partner with information that is actionable without evaluation of individual EPCIS events.

Using ReferenceModel 2, the trading partner could query the blockchain to retrieve all states of the package, lot, product or shipment. The states would show whether the manufacturer, or anyone else in the supply chain, had posted an event that would render the product unusable (recall, damage, expired, etc.). **Figure 14** diagrams the verification process for the sample wholesaler and dispenser.

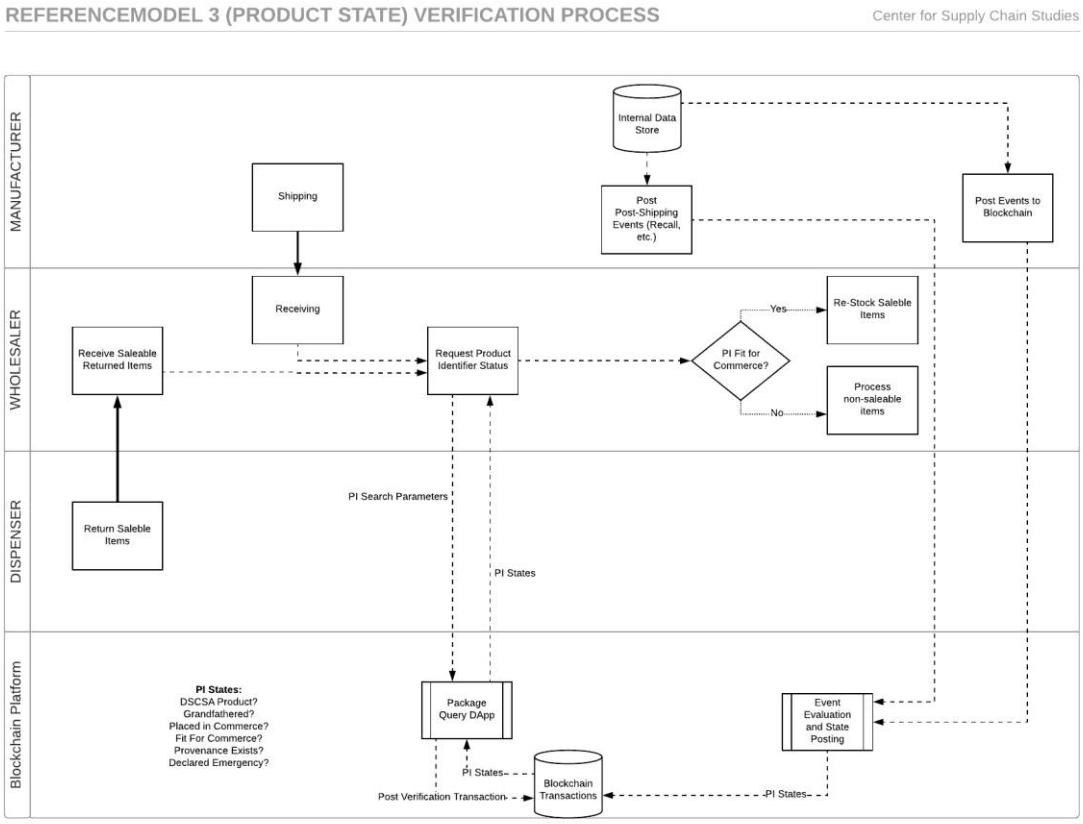

Figure 14:
ReferenceModel 3 – *Verification*

ReferenceModel 3:
The Data

The data depicted in **Figure 15** is non-normative and was used to experiment with placing the TI data on the blockchain. It shows the data that each trading partner holds internally and the data that is posted to the blockchain platform.

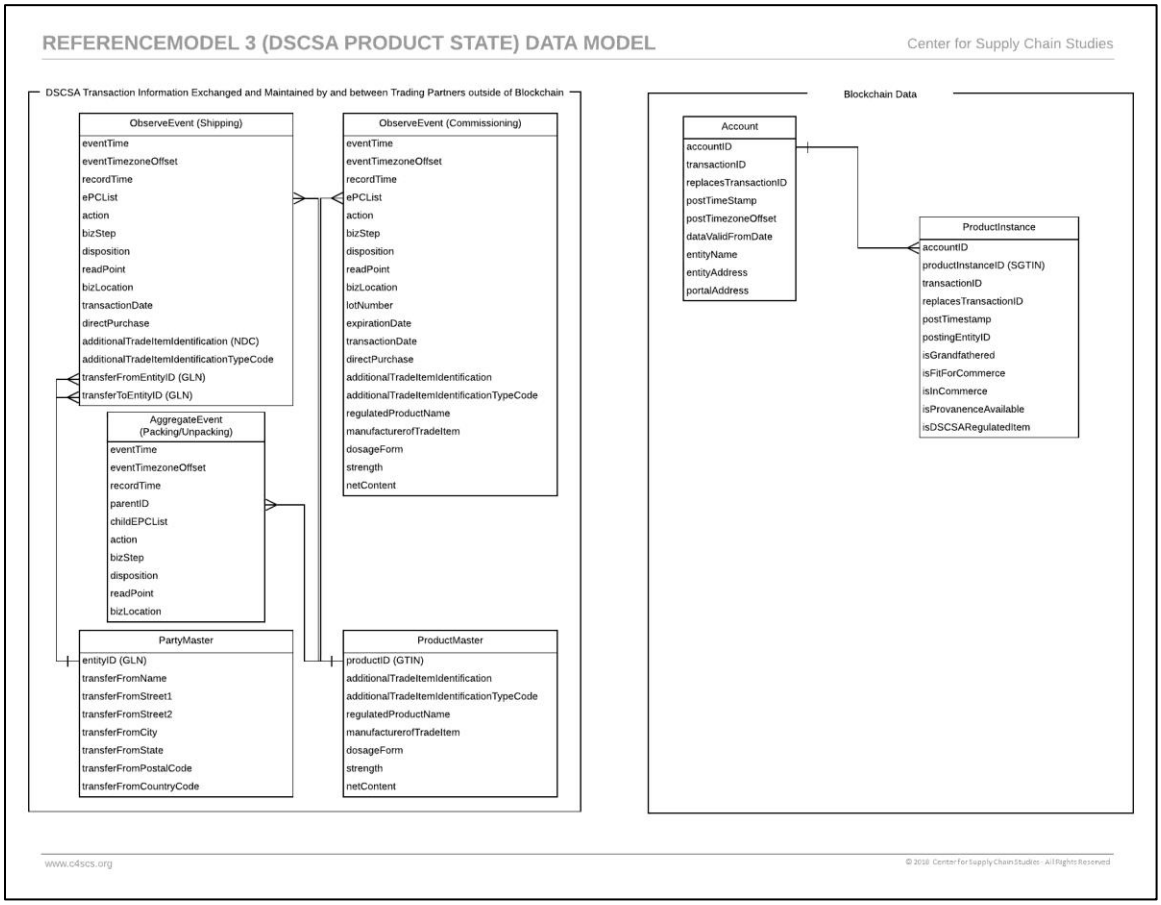

Figure 15:
ReferenceModel 3 – *Trading Partner and Blockchain Data*

ReferenceModel 3+:
The Data

The data depicted in **Figure 16** is non-normative and was used to experiment with placing the TI data on the blockchain. It expands on the "state" concept of ReferenceModel 3 by logically grouping data that may be interesting to query and provides "state" information at the correct group level efficiently.

For example: Determining whether a product is a DSCSA regulated drug is recorded at the product level ("isDSCSARegulatedItem") and not repeated for each package of the product (at the Product Instance level). It shows the data that each trading partner holds internally and the data that is posted to the blockchain platform.

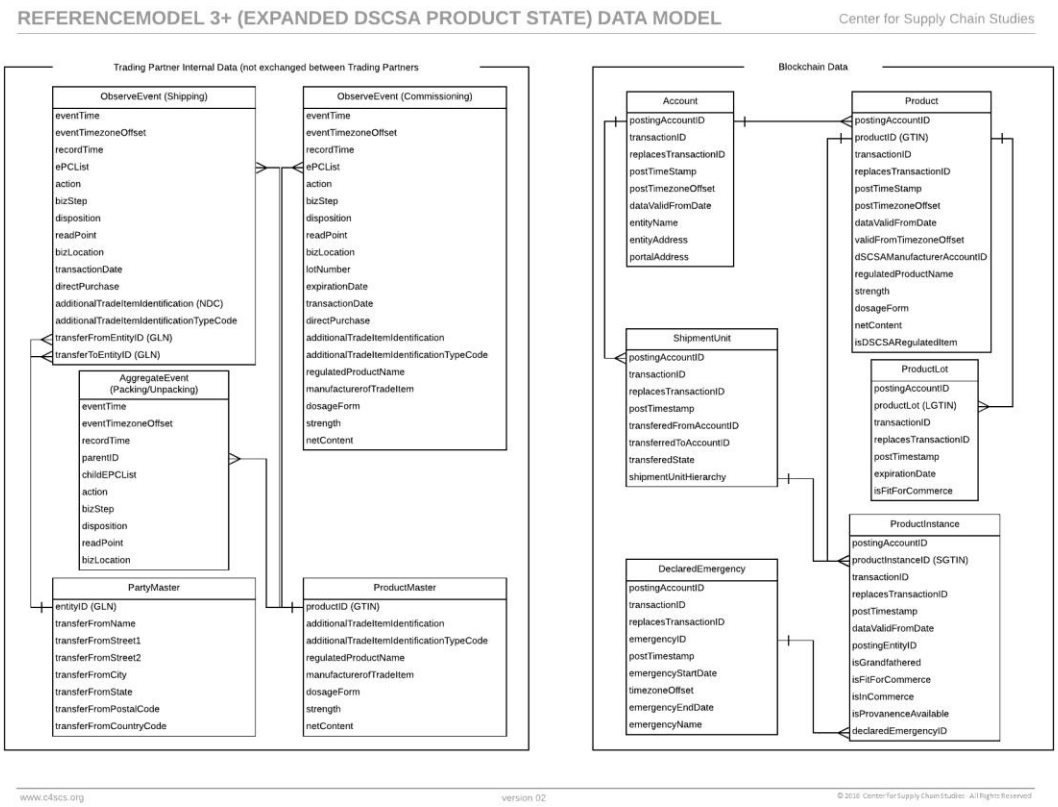

Figure 16:
Expanded data model to support additional value

Evaluating the ReferenceModels

As this was an exploratory Study, we expected to discover and consider different means to utilize blockchain technology to support DSCSA requirements. We hoped this type of examination would provide a platform for learning about supply chain processes, the DSCSA, blockchain technology and the intersection of all three.

All three of this Study's ReferenceModels incorporated different strategies for leveraging blockchain technology – each exposed technical challenges and provided insights into the difficulties of accurately managing product at the serialized package level and at a speed needed by the supply chain.

Not surprisingly, with each strategy we encountered a common set of obstacles that are general to transacting business using a common, visible platform such as blockchain. The challenge of searching for information – while at the same time constraining access to that information to trading partners that have had ownership of the package – is a difficult task (*even with the knowledge that the information may exist*). In all models, this resulted in a multi-step process of evaluating the query and determining whether the querying party should have access to the data.

The following evaluation provides an overview of the Study team's insights into the challenges and benefits of each ReferenceModel. The final take-away from the group is that many of the industry's current regulatory challenges may be successfully addressed as blockchain (and supporting) technology continues to evolve.

With an overarching awareness of the importance of supply chain integrity and protection, we believe it is possible to provide effective, secure and innovative ways of doing business with blockchain technology.

The models and DSCSA requirements

The following requirements are the main data exchange requirements of the DSCSA. The evaluation of the three ReferenceModels reflect the commentary of the Study team participants.

Table 3: *DSCSA Requirements and the Models*

	ReferenceModel 1 TI/TS Ledger	ReferenceModel 2 Directory	ReferenceModel 3 Package State	ReferenceModel 3+ Expanded States
Passing TI to next trading partner	Via direct transfer of EPCIS Events	Via direct transfer of EPCIS Events	Via direct transfer of EPCIS Events	Via Shipment Unit blockchain entry
Saleable Returns Verification	Via bizStep of "commissioning" in the posted *ObserveEvent*	1. Retrieve portal addresses from blockchain 2. Via the manufacturer (or repackager) portal or EPCIS repository return of commissioning event	Via *isInCommerce* and *isFitForCommerce* flags in ProductInstance	Via is*InCommerce* and *isFitForCommerce* flags in ProductInstance
Retrieving previous TI back to manufacturer	Via a combination of Observe Events (commissioning and shipping) and Aggregation Events (packing)	Via series of blockchain data queries and query submissions to the portal addresses provided from the blockchain response	Via *isProvananceAvailable* flag (know that an unbroken chain of ownership exists). Retrieve TI data via querying the account's portal address as in ReferenceModel 2.	Via Shipment Unit, Product, ProductInstance data posted to blockchain
Recall	Manufacturer can post Observe Event with bizStep = "inspecting" and disposition = "recalled"	Upon TI retrieval *(see retrieving TI above)*, manufacturer can include an Observe Event with bizStep = "inspecting" and disposition = "recalled"	Manufacturer sends Recall Event data in form of parameters to a DApp which evaluates data and sets *isFitForCommerce* flag in Product Instance blockchain entry	Manufacturer sends Recall Event data in form of parameters to a DApp which evaluates data and sets *isFitForCommerce* flag in Product Lot dataset or Product Instance blockchain entry
Related Requirements				
Proof that data hasn't been altered	All TI data is on the blockchain and is unalterable	Hash value for the TI data is posted on the blockchain and can be matched against the calculated hash value on TI data, retrieved via the trading partner portal address	DApp posts blockchain entries based on consensus rules and data provided as parameters by authoring entity	DApp posts blockchain entries based on consensus rules and data provided as parameters by authoring entity

Measuring the models against stakeholder needs

The following notable needs were identified by the supply chain stakeholders in the Study. The evaluation of the three ReferenceModels reflect the commentary of the Study team participants.

Table 4: *Supply Chain Stakeholder Needs and Models*

	ReferenceModel 1 TI/TS Ledger	ReferenceModel 2 Directory	ReferenceModel 3 Package State	ReferenceModel 3+ Expanded States
MANUFACTURER				
Eliminate verification queries	Yes	No	Yes	Yes
WHOLESALER				
Remove need for separate TI events outside of blockchain	No	No	No	Yes
Provide consolidated logistic unit hierarchy	No	No, but possible	No	Yes
DISPENSER				
Reduce verification queries	Yes, 1 query per package	No, 1 portal address query and one TI retrieval Query. Could be able to manage queries for a list of packages.	Yes, 1 query per package	Yes, 1 query per shipment (for 1st wholesaler), 1 query per package for all others.
ALL				
Individual control of authored data access	No, TI data is posted and accessed based on industry set rules	Yes, TI is passed via EPCIS events and all Trading parties query your portal individually	Partial, package state(s) are determined by implemented industry set rules	Partial, package, product and shipment state(s) are determined by implemented industry set rules

The models and Study goals

The following goals were determined at the beginning of the Study. The evaluation of the three ReferenceModels reflects the commentary of the Study team participants.

1. Establishing an electronic connection between non-adjacent trading partners
2. Establishing trust between these trading partners
3. Sharing required data without inadvertently exposing proprietary information
4. Reducing the potential activity required of trading partners
5. Designing for expansion beyond DSCSA compliance
6. Funding the architecture.
7. Reducing risk

Table 5 depicts how the models performed against the initial seven goals of the Study.

Table 5: *Study Goals and the Models*

	ReferenceModel 1 TI/TS Ledger	ReferenceModel 2 Directory	ReferenceModel 3 Package State	ReferenceModel 3+ Expanded States
Electronic Connection	Simplified for blockchain, however, still need individual connections between trading partners (RM02 & RM03).			Individual connections not needed.
Trust	Managed through permissioned access to posted data	Managed by each trading partner portal	Managed by Industry consensus on DApps	Managed by Industry consensus on DApps
Confidentiality				
Efficiency	Simple post of event data to blockchain to facilitate TI gathering, however, may require separate send of TI data directly to next trading partner.	Requires separate send of TI data directly to next trading partner. Retrieval of TI data is a 2-step process (1. Retrieve the portal addresses, 2. Query the portals). May benefit from a bulk query (list of serialized items to verify or retrieve).	Up-front work of evaluating the event data is performed by the DApp(s) on the blockchain. Trading partners retrieve and check the latest states(s) for a package instead of a series of events.	Up-front work of evaluating the event data is performed by the DApp(s) on the blockchain. Trading partners retrieve and check the latest states(s) for a package instead of a series of events. Additional efficiency of determining product level and lot level questions with one query.
Expanded value	This model could be expanded by adding new datasets or adding to the existing ones. As the Observe Event dataset contains elements that are not logically grouped, there could be some issues adding new datasets.	This model could be expanded by adding additional datasets and API (s) to trading partner portals. However, making the community aware that a new feature or dataset is available may be difficult.	This model has been expanded to create ReferenceModel 3+.	Can expand to include additional level of information for products (temperature handling instructions), lots (recall), shipments.

	ReferenceModel 1 TI/TS Ledger	ReferenceModel 2 Directory	ReferenceModel 3 Package State	ReferenceModel 3+ Expanded States
Funding	Funding models for the shared infrastructure are the same for all ReferenceModels. Membership fees, fees per transactions and utilization of stable cryptocurrencies to fund necessary processing and storage usage. Funding for company-specific repositories will be the responsibility of each trading partner.			
Risk	If trading partners have different interpretations of a series of events a package was involved in. Secondary risk is synchronizing trading partner movement to the same version of event structure. Timing of event posting could cause delays for trading partners processing.	**1**. If trading partner portal is offline, data cannot be verified. **2.** If trading partner accessing portal cannot recall procedures for each repository, performance could be degraded, and labor hours lost.	Risk is mitigated by the industry-agreed DApps that evaluate the events to determine the state(s) of each package. There is risk of missing a state change if the event is not sent to the blockchain DApp(s).	Risk is mitigated by the industry-agreed DApps that evaluate the events to determine the state(s) of each package. There is risk of missing a state change if the event is not sent to the blockchain DApp(s).

Measuring the models against the challenges

The challenges listed in **Table 6** were identified throughout the Study. The evaluation of the three ReferenceModels reflect the commentary of the Study team participants.

Table 6: *Challenges and the Models*

	ReferenceModel 1 TI/TS Ledger	ReferenceModel 2 Directory	ReferenceModel 3 Package State	ReferenceModel 3+ Expanded States
		DSCSA		
Multi-link transactions (M-W-D, M-W1-W2-D)	EPCIS events are passed outside of the blockchain. To provide access to event data on an individual package, events are stored at the package level. *eg: individual commissioning events.*	EPCIS events are passed outside of the blockchain.	EPCIS events are passed outside of the blockchain. Stores the "states" of the package as it moves through the supply chain.	Provides shipment hierarchy for each shipment along a package's route. Provides information at the product and Lot level that can be shared with subsequent trading partners.
SEC. 203(g)(1)(E) of the DSCSA – Retrieving previous TI data (2023)	Each trading partner's TI data is stored and can be shared with other trading partners based on industry set rules.	To provide query access to retrieve TI data on an individual package, package level ID is associated with the creating account ID.	Each trading partner's events are provided to a blockchain DApp, which stores the new "state(s)" of the package.	Data is available at many levels (shipment, product, Lot and instance) to respond to queries. DApp(s) post the information and new "state(s)". A portal address is available to query the authoring company directly.
2019, Verification of saleable returns	Commissioning data for each package is available.	Commissioning data for each package is available through the manufacturer's portal.	The *"isInCommerce"* indicator is set for each package.	The *"isInCommerce"* indicator is set for each package.

	ReferenceModel 1 TI/TS Ledger	ReferenceModel 2 Directory	ReferenceModel 3 Package State	ReferenceModel 3+ Expanded States
Supply Chain				
Multiple company identifiers	This challenges all models. It can be solved either by strictly using a single GLN or blockchain Account ID per company or by introducing a company hierarchy look up service.			
Data Access Governance	Must be managed by rules set by industry consensus.	Is managed by individual trading partners in response to TI data queries.	Must be managed by rules set by industry consensus.	Must be managed by rules set by industry consensus.
Blockchain				
Obfuscating data on the Blockchain	This challenges all models. The ability to hide data from a blockchain participant while allowing them to query for data requires special capabilities of a blockchain. The team discussed and experimented with DApp oracles to encrypt data, zero knowledge proofs and other mechanisms. Some blockchain platforms are developing mechanisms to allow querying and obfuscation through special on blockchain processes.			
Data storage limitations	Quite a bit of data is stored in this model. However, private blockchain platforms (vs public blockchains) can manage larger amounts of data.	Minimal data is stored in this model.	Minimal data is stored in this model.	Data is stored across a data model. Each blockchain transaction stores minimal data.
Multiple Platforms	This challenge affects all models. If industry data is spread across multiple blockchain platforms, it is unknown how industry set data access rules would be enforced. There are blockchain/database hybrid solutions (BigchainDB) and other blockchain-like platforms that might be useful. A single platform may be needed in the near term as the technology evolves and solutions are developed.			
Cost	This challenge affects all models. Whether blockchain token or cryptocurrency usage will be acceptable to the industry, traditionally negotiated contract with service providers or some mix of each will emerge to settle the cost/funding model.			

Other Study findings and thoughts

Public and private blockchains

It is generally thought that private, permissioned blockchain platforms are safer than public platforms. That public platform suffers from the following problems:

1. **Performance and storage bloat.** Public blockchains will be subject to a wide range of transactions unrelated to the pharma supply chain. They will create contention for rapid processing of transactions, slowing the processing time. It will also create a much large data storage requirement because storing the entire blockchain would include the millions of non-pharma transactions.
2. **Governance risk.** Over time, blockchain governing groups make changes to their blockchains to address various issues that may arise. In a public blockchain, these changes may not be agreeable to the pharma trading partners, but they may be outvoted. In a private blockchain, the rules and changes will be determined solely by the pharma trading-partner members.
3. **Increased risk of compromise.** Nefarious actors could attack the blockchain whether it is public or private. But, the public blockchain is out in the open for them to study to determine vectors of attack. A private blockchain would be less visible (*so that many nefarious actors might not even be aware of it*) and afford less opportunity for planning an attack.

Protecting the confidentiality of information on blockchains

Most current blockchain platforms make transactions posted to a blockchain visible to all entities that are connected to the blockchain. This visibility is a double-edged sword. It allows anyone to determine if data has been tampered with (by checking the block hash values), but it also allows any connected entity to read posted data and assess the blockchain data for patterns.

All three reference models specify that data posted on the blockchain be obfuscated. However, they don't specify *how*. The team has explored encryption, digital signatures and in one instance, zero knowledge proofs. Additional models not considered here use still other techniques to provide the necessary confidentiality. All have merit, and all have drawbacks in terms of key management, additional services needed, etc. The team also recognizes the challenges of establishing confidentiality in an open platform (even in private/permissioned platforms) and the issues that may be encountered in key archiving and transferal as part of mergers or acquisitions.

Governance

Regardless of the solution selected to address DSCSA (*whether it includes a blockchain component or not*) the requirement of an interoperable solution imposes a significant demand on the industry to establish the governance rules needed for compliance. This calls for developing a consensus among all the stakeholders on dozens of rules of engagement – each of whom may require hundreds of decisions to formulate.

Because the industry is composed of hundreds of trading partners ranging from small to huge, weak to powerful, sophisticated to unsophisticated – providing a wide variety of services along the supply chain path for thousands of products and achieving this consensus will be a difficult and time-consuming effort. Even if all parties were to agree today to implement one of the ReferenceModels™ described above, it will take a long time to establish a consensus on each of these hundreds of decisions that will need to be made.

Next steps

This exploratory Study documented and provided opportunity to explore the supply chain, DSCSA language and blockchain technology. Several challenges were identified, and potential design alternatives thought through. This was the *first step* in readying supply chain stakeholders and solution providers to define the interoperable system needed to satisfy the requirements of the "Enhanced Drug Distribution System" outlined in the DSCSA.

As supply chain stakeholders are currently working through serialization of drug products, there are not enough of them to fully pilot any of the ReferenceModel designs. The next steps are to move from a simulated environment to test environments where the technology can be explored using test or simulated data. This phase will give clarity on implementation issues – testing potential back-end integration and solution-to-solution interoperability. Once the stakeholders begin to converge on single model and can engage in connecting internal systems to a test environment, full pilots and implementations will follow.

Pilots that connect trading partners will provide the information needed to determine standards and guideline development, easing the development of production systems.

Appendix

Terms

DSCSA: Drug Supply Chain Security Act[25]

Tracing Requirement: Effective November 2023, the DSCSA law reads: ``*SEC. 203(g)(1)(E) The systems and processes necessary to promptly facilitate gathering the information necessary to produce the transaction information for each transaction going back to the manufacturer, as applicable, shall be required."*

Obfuscation: For the purposes of this white paper, obfuscation means masking or otherwise making the value of the attributes unknowable to parties other than the creator and those parties. The creator or their proxy give the capability to unmask or otherwise know the value of the attributes.

Trading Partner: Participant in the US drug supply chain. The DSCSA identifies the following trading partner types (see definitions in the DSCSA[26]):

- Manufacturer
- Repackager
- Wholesale Distributor
- Third Party Logistics Provider (3PL)
- Dispenser

Blockchain oracle: A specialized distributed application (DApp) provided as a service to allow blockchain distributed applications to access data outside of the blockchain. *For example, an oracle could provide ambient temperature data from a trusted weather bureau.*

Service Provider: A company that provides data access services to supply chain participating companies.

Transaction Information: Defined in the DSCSA as:

TRANSACTION INFORMATION —The term 'transaction information' means—
"(A) the proprietary or established name or names of the product;
"(B) the strength and dosage form of the product;
"(C) the National Drug Code number of the product;
"(D) the container size;
"(E) the number of containers;
"(F) the lot number of the product;
"(G) the date of the transaction;
"(H) the date of the shipment, if more than 24 hours after the date of the transaction;
"(I) the business name and address of the person from whom ownership is being transferred; and
"(J) the business name and address of the person to whom ownership is being transferred."

Transaction Statement: Defined in the DSCSA as:

TRANSACTION STATEMENT. — The 'transaction statement' is a statement, in paper or electronic form, that the entity transferring ownership in a transaction —
"(A) is authorized as required under the Drug Supply Chain Security Act;
"(B) received the product from a person that is authorized as required under the Drug Supply Chain Security Act;
"(C) received transaction information and a transaction statement from the prior owner of the product, as required under section 582;
"(D) did not knowingly ship a suspect or illegitimate product;
"(E) had systems and processes in place to comply with verification requirements under section 582;
"(F) did not knowingly provide false transaction information; and
"(G) did not knowingly alter the transaction history."

[25] https://www.fda.gov/drugs/drugsafety/drugintegrityandsupplychainsecurity/drugsupplychainsecurityact/default.htm
[26] https://www.gpo.gov/fdsys/pkg/PLAW-113publ54/pdf/PLAW-113publ54.pdf

Use of SWOT analysis

The Study team evaluated the ReferenceModels based on their understanding of the fit of the model DSCSA compliance, supply chain operations blockchain technology and governance. The team also evaluated the ReferenceModels using the initial goals that were set at the beginning of the Study. Lastly, we evaluated based on traditional SWOT (Strengths, Weaknesses, Opportunities and Threats) to give an overall impression of the ReferenceModels.

Definition of SWOT analysis (or SWOT matrix)[27]

SWOT analysis is a strategic planning technique used to help a person or organization identify the *Strengths*, *Weaknesses*, *Opportunities*, and *Threats* related to business competition or project planning.[1] It is intended to specify the objectives of the business venture or project and identify the internal and external factors that are favorable and unfavorable to achieving those objectives. Users of a SWOT analysis often ask and answer questions to generate meaningful information for each category to make the tool useful and identify their competitive advantage.

Strengths and Weakness are frequently internally-related, while Opportunities and Threats commonly focus on environmental placement.

- **Strengths:** Characteristics of the business or project that give it an advantage over others
- **Weaknesses:** Characteristics of the business that place the business or project at a disadvantage relative to others
- **Opportunities:** Elements in the environment that the business or project could exploit to its advantage
- **Threats:** Elements in the environment that could cause trouble for the business or project

ReferenceModel actors

Each ReferenceModel represents a simple supply chain adhering to a specific data sharing strategy to support DSCSA compliance. ReferenceModels were created to explore alternate strategies or methods of making DSCSA supporting data available to each depicted trading partner. They demonstrate enough product movement variation and information sharing to provide insight into how data-sharing strategies and associated rules could work to support DSCSA compliance.

The processes that are exercised by each trading partner do not represent the exhaustive list of processes that take place. Rather, they were created to exercise the data sharing strategies and rules and to provide enough generated data to explore and compare the strategies.

The following actors were used uniformly in the ReferenceModels to aid in comparing the outcome of the strategies.

Manufacturer 1 (identified as M001): The simulated manufacturer creates the pharmaceutical product by Lot, packages it into cases and then packages those cases onto pallets. Pallets are put away in storage and picked to fulfill large wholesaler orders. Following GS1 EPCIS best practices, data sets extracted from Commissioning, Packing and Shipping events are created and processed according to the model's data sharing strategy.

Wholesaler 1 (identified as W001): This simulated wholesaler represents a large, high throughput, national wholesaler that purchases directly form the manufacturer. It receives the shipment at the pallet level (simulated scan of pallet SSCC), breaks down the pallet to individual cases and breaks down each case and puts away the individual trade items. To reflect realities in a high throughput wholesale environment, the cases and trade items are not scanned during unpacking. Trade Items are scanned at the time of order picking and verified against data made available by the design of the ReferenceModel (reflecting the model's data sharing strategy). Trade items are packed into reusable totes and shipped to either the regional wholesaler (W002) or the dispenser (D001 or D002).

[27] Source: https://en.wikipedia.org/wiki/SWOT_analysis

Wholesaler 2 (identified as W002): This represents a simulated regional wholesaler that purchases from a large national wholesaler (W001). It receives shipments of totes from the national wholesaler and scans the tote upon receipt (simulated scan of tote SSCC). It then breaks down the tote to individual trade items and puts away the individual trade items. Trade Items are scanned at the time of order picking and verified against data made available by the design of the ReferenceModel (*reflecting the model's data sharing strategy*). Trade items are packed into reusable totes and shipped to the dispenser (D001 or D002).

Dispenser 1 (identified as D001): This simulated dispenser represents a hospital facility that purchases from a large national wholesaler (W001) or regional wholesaler (W002). It receives shipments of totes from the national or regional wholesaler and scans the tote upon receipt (simulated scan of tote SSCC). It then breaks down the tote to individual trade items and puts away the individual trade items. The individual trade items are scanned at dispense and verified against data made available by the design of the ReferenceModel (*reflecting the model's data sharing strategy*).

Dispenser 2 (identified as D002): This simulated dispenser represents a large retail pharmacy chain that purchases from a large national wholesaler (W001). It receives shipments of totes at its warehouse and self-distributes to the retail store pharmacy. It then scans the tote upon receipt (*simulated scan of tote SSCC*) and then breaks down the tote to individual trade items and puts away the individual trade items. The individual trade items are scanned as the trade items are picked for pharmacy delivery and verified against data made available by the design of the ReferenceModel (*reflecting the model's data sharing strategy*).

Other ReferenceModel Trading Partners: As the team discussed additional processes and trading partner relationships, partial models were created to explore the data sharing strategies and how they might affect or be affected by these other trading partners in the supply chain. The ReferenceModels published here include only the above trading partner actors. Other trading partners explored were:

- **Virtual Manufacturer (identified as VM001):** This actor is the manufacturer of record in DSCSA terms, however, they have outsourced trade item production to a Contract Manufacturer.
- **Contract Manufacturer (identified as CM001):** This actor manufactures the trade item on behalf of the manufacturer. They also provided needed DSCSA data on behalf of the Manufacturer.
- **Third Party Logistics Provider (identified as 3PL001):** This actor transports shipments from the manufacturer to the wholesaler. It takes possession of the shipment, but not ownership.
- **Reverse Distributor (RD001):** This actor receives trade items destined for destruction. Several sub-models depicted reverse distributors receiving product from a wholesaler, notifies the manufacturer and destroys the trade item.
- **Repackagers:** Although the repackaging operation was discussed, no ReferenceModels were built reflecting this unique process of removing drug product from the manufacturer's packaging, combining it with drug product from other trade items and repackaging into new (different count sized) trade items.

Scenarios used to determine quantity and volume of transactions

Supply Chain Scenario #1:
Manufacturer to Wholesaler to Dispenser

Manufacturer 001 manufacturers and sells Product 01 in 60 count bottles in lots of 40,000. They are packed into 20 count cases. Pallets contain 100 cases.

To describe the production of a Lot in EPCIS terms, the Manufacturer would record:

- 1 Commissioning event listing the 40,000 GTIN/Sn of each bottle
- 2,000 Commissioning events (1 for each Case)
- 2,000 Packing events (1 for each Case)
- 20 Commissioning events (1 for each Pallet)
- 20 Packing events (1 for each pallet)

A Wholesaler orders 100 cases (1 Pallet) of product 01. To describe the items in that shipment, the manufacturer would record and send to the Wholesaler:

- 1 Commissioning event listing the 2,000 units, 100 cases and 1 pallet sold
- 100 Packing events (1 for each case)
- 1 Packing event (for the pallet)
- 1 shipping event (for the pallet)

The Wholesaler would record:

- The 103 events sent by the Manufacturer
- 1 Receiving event (for the Pallet)
- 1 Unpacking event (for the pallet)

A Dispenser orders 5 bottles of Product 01 from the Wholesaler. The Wholesaler would record:

- 1 Unpacking event (for the case)
- 1 Commissioning event (for the Tote)
- 1 Packing event (for the Tote and 5 bottles)
- 1 Commissioning event (for the 5 bottles, extracted from the Manufacturer's Commissioning event)
- 1 Shipping event (for the Tote)

The Wholesaler would send the Dispenser:

- 1 Commissioning event (for the Tote)
- 1 Packing event (for the Tote and 5 bottles)
- 1 Commissioning event (for the 5 bottles, extracted from the Manufacturer's Commissioning event)
- 1 Shipping event (for the Tote)

The Dispenser would record:

- The 4 events sent by the Dispenser
- 1 Receiving event (for the Tote)

Supply Chain Scenario #2:
Manufacturer to Wholesaler 1 to Wholesaler 2 to Dispenser

Manufacturer 001 manufacturers and sells Product 01 in 60 count bottles in lots of 40,000. They are packed into 20 count cases. Pallets contain 100 cases.

To describe the production of a Lot in EPCIS terms, the Manufacturer would record:

- 1 Commissioning event listing the 40,000 GTIN/Sn of each bottle
- 2,000 Commissioning events (1 for each Case)
- 2,000 Packing events (1 for each Case)
- 20 Commissioning events (1 for each pallet)
- 20 Packing events (1 for each pallet)

A national Wholesaler orders 100 cases (1 Pallet) of product 01. To describe the items in that shipment, the manufacturer would record and send to the Wholesaler:

- 1 Commissioning event listing the 2,000 units, 100 cases and 1 pallet sold.
- 100 Packing events (1 for each case)
- 1 Packing event (for the pallet)
- 1 shipping event (for the pallet)

The national Wholesaler would record:

- The 103 events sent by the Manufacturer
- 1 Receiving event (for the pallet)
- 1 Unpacking event (for the pallet)

A regional Wholesaler orders 3 cases of product 01 from the national Wholesaler. The national Wholesaler would record:

- 1 Commissioning event derived from the Manufacturer's that only includes the 3 cases sold to the regional wholesaler
- 3 Packing events derived from the Manufacturer's that only includes the cases and the contents of those cases sold to the regional wholesaler
- 1 Shipping event (for the cases)

The regional Wholesaler would record:

- The 5 events sent by the national Wholesaler
- 3 Receiving events (for the Cases)

A Dispenser orders 5 bottles of Product 01 from the regional Wholesaler. The regional Wholesaler would record:

- 1 Unpacking event (for the case)
- 1 Commissioning event (for the Tote)
- 1 Packing event (for the Tote and 5 bottles)
- 1 Commissioning event (for the 5 bottles, extracted from the national Wholesaler's Commissioning event)
- 1 Shipping event (for the Tote)

The regional Wholesaler would send the Dispenser:

- 1 Commissioning event (for the Tote)
- 1 Packing event (for the Tote and 5 bottles)
- 1 Commissioning event (for the 5 bottles, extracted from the national Wholesaler's Commissioning event)
- 1 Shipping event (for the Tote)

The Dispenser would record:

- The 4 events sent by the Dispenser
- 1 Receiving event (for the Tote)

U.S. FOOD & DRUG ADMINISTRATION

Should this drug package or case have a product identifier under the

Drug Supply Chain Security Act?

Determine whether the drug is a product covered under the Drug Supply Chain Security Act (DSCSA). Covered products are defined as human prescription drugs in finished dosage form and are required to have a product identifier on each package. Most prescription drugs are covered under the law, but there are a few exceptions.

YES, the product is covered under DSCSA

NO, the product is not covered under DSCSA

Product identifier is not required.

Which trading partner are you under DSCSA?

I'm a manufacturer selling product

As of 11/27/2018 – product identifier is required.

Products packaged before 11/27/18 do not need product identifiers and can continue to move through the supply chain.

See Grandfathering Policy and Product Identifier Compliance Policy

I'm a repackager selling product

As of 11/27/2018 – product identifier is required.

Products packaged before 11/27/18 do not need product identifiers and can continue to move through the supply chain.

See Grandfathering Policy

I'm a repackager buying product

Do you have documentation that the product was packaged by a manufacturer or other repackager before 11/27/2018?

YES

The product is grandfathered. You can buy it without a product identifier.

NO

The product is not grandfathered. It should have a product identifier unless it is subject to a waiver or exemption. Confirm with the product manufacturer or other repackager.

See Grandfathering Policy

I'm a wholesale distributor or dispenser buying or selling product

Do you have documentation that the product was packaged by a manufacturer or repackager before 11/27/2018?

YES

The product is grandfathered. You can buy and sell it without a product identifier.

NO

The product is not grandfathered. It should have a product identifier unless it is subject to a waiver or exemption. Confirm with the product manufacturer or repackager.

See Grandfathering Policy

If you are still unsure whether a prescription drug should have a product identifier, contact the manufacturer or repackager.

For definitions in the Federal Food, Drug, and Cosmetic Act, see section 581(13) for product, section 581(14) for product identifier, 581(7) for homogenous case and section 581(11) for package. See the Grandfathering Policy for the type of documentation that would identify if a product is grandfathered.

GDPR Compliance:
What You Need to Know

Amy B. Goldsmith, Esq.
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From: Amy B. Goldsmith
To: Section Chair, NYSBA, Food, Drug and Cosmetic Section
Date: January 7, 2019

On May 25, 2018, the European Union has enacted a new General Data Protection Regulation (GDPR) regarding how businesses, wherever they are located around the world, must manage the personal data of European "data subjects."

What is personal data? It is *any* information relating to an identified or identifiable natural person.

The GDPR applies to every situation in which any type of business (for example, food, drug or cosmetic companies, online or brick and mortar retail stores, landlords, accountants, real estate and insurance brokers, publishers, consumer goods manufacturers, healthcare companies) collects personal data from a "data subject" - European citizens and residents as well as nationals of other countries who are in the borders of the EU when the personal data is processed. Personal data may be collected through a form on an app, via a corporate website, at the point of sale of a product or at a conference. For instance, if a business has a contact form on their website or at the point of sale, and individuals located in the EU are not automatically excluded (i.e., if the contact form has a space for country, and persons checking "EU" or an EU member nation are permitted to go to the next step and complete the form), then the business is subject to the GDPR.

If a business is in negotiations with EU data subjects, and the business is gathering personal data about individuals, then the GDPR applies. Basically, if there is any action that a business takes or may in the future take in connection with EU data subjects where personal data is gathered (such as a person's name, address or national identification number), the GDPR applies. The GDPR also applies if a business established outside the EU is processing personal data in the EU, collecting or processing personal data of EU data subjects, or has a temporary or permanent location in the EU.

Key Provisions

Upholding and enforcing the privacy rights of citizens of the European Union is the critical focus of the GDPR.

- Right to revoke prior consent: An EU data subject may revoke prior consent regarding your business's use of personal data

- Right to be forgotten: An EU data subject has the right to demand that your business delete all of the information you've collected about her

- Right to rectification: An EU data subject has the right to correct information that it previously provided

- Right to access personal data: An EU data subject may demand to know what data your business holds about him, how you use that data, and where it is stored

- Right to move personal data: An EU data subject has the right to demand that you move personal data to another provider

- Notification of data breach: The business must notify EU data subjects within 72 hours of a data breach that may affect their personal data

Key Actions

These are some of the actions that businesses are taking to comply with the GDPR:

- New GDPR Policy: businesses are posting new GDPR privacy policies on their websites and apps

- Opt-in: any form used to gain consent to collect personal data of EU data subjects must explicitly list each and every task that the person is permitting the business to do, such as emailing the EU data subject, sending marketing material, sharing personal data with others, using cookies, using personal data to retarget social media campaigns, and analytics and tracking

- Continued Consent: existing EU data subjects are being contacted and presented with the new opt-in forms and the option to entirely opt-out

- Separate Data Storage: given the rights to move personal data, revoke consent, and be forgotten, maintaining EU data subjects' personal data apart from that of citizens of other nations is a best practice. Businesses may also hold the personal data of UK citizens in another location since it's not clear whether the UK will adopt the GDPR, or a similar regulation, after Brexit. Your client may choose to have a sophisticated third-party vendor hold all of the personal data and be legally responsible for, and indemnify your business with respect to, GDPR compliance

- Responsible Persons: each business not located in the European Economic Area (EEA) is required to appoint (1) a representative within the EEA to be its primary point of contact with the European authorities and (2) a contact person at your business to serve as the data protection contact for EU data subjects

If your client’s business collects personal data from European data subjects, then understanding the GDPR and implementing new protocols are critical to properly managing their personal data. Working with counsel who partners with European privacy experts is one way to navigate this new system.

APPENDIX A

EUROPEAN UNION and EEA

EU Countries		EEA Countries
Austria	Italy	Liechtenstein
Belgium	Latvia	Iceland
Bulgaria	Lithuania	Norway
Croatia	Luxembourg	
Cyprus	Malta	
Czech Republic	Netherlands	
Denmark	Poland	
Estonia	Portugal	
Finland	Romania	
France	Slovakia	
Germany	Slovenia	
Greece	Spain	
Hungary	Sweden	
Ireland	United Kingdom (pre-Brexit, perhaps post too)	

APPENDIX B

Personal Data

- Name
- Date of birth
- Email Address
- Residence Address
- Phone
- Citizenship information
- Residency information
- Race
- Gender
- Religion
- Health
- Financial information
- Purchasing history
- IP addresses
- Cookies

“data from which a living **individual** can be identified or identifiable (by anyone), whether directly or indirectly, by all means reasonably likely to be used”

Living Individual = Data Subject

APPENDIX C

Where and how do clients house personal data?

- Existing databases of customers, vendors, business contacts and others from contact forms

  - DMS
  - Email
  - Disaster Recovery Repositories
  - Communications with Government Agencies
  - Contact Management System
  - Billing System
  - Insurance carriers and brokers
  - Electronically Stored Information Systems
  - Phone System
  - Cookies
  - Tracker™
  - Docketing/Calendaring systems

- New Consent Forms from Data Subjects

- Payment (credit card, PayPal)

APPENDIX D

How should clients protect and safely share personal data?

- Passwords: the PD is kept in a password protected environment and is accessible only to those employees who must have access as part of their business function

- No Downloads: the PD should not be downloaded to a laptop, phone, thumb drive, or any other storage device and should not be printed unless it's necessary

- Safe Password Exchange: the passwords should be exchanged person to person, phone to phone (not voice mail) NOT BY email or text or voice mail

- Sharing: the document containing the PD should only be shared with specified third parties by authorized individuals

- Secure Hosted Environment: these services could be used for sharing the PD document (Dropbox, WeTransfer, etc.)

- Breach Notification: if the PD is breached, the client must notify the Data Subject within 72 hours of the client's knowledge of the breach; the client may wish to use a third party vendor

APPENDIX E

How do the data subjects access their personal data?

The client should implement a system to respond to a Data Subject's request to do any of the following:

- Update personal data
- Revoke permission to send marketing materials per each line item
- Object to the client's handling of personal data
- Instruct deletion of personal data but first confirm if the client has a legal obligation to maintain PD that in legal's view supersedes GDPR; health records must be maintained, for instance

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Czech Republic	Netherlands	
Denmark	Poland	
Estonia	Portugal	
Finland	Romania	
France	Slovakia	
Germany	Slovenia	
Greece	Spain	
Hungary	Sweden	
Ireland	United Kingdom (pre-Brexit, perhaps post too)	

APPENDIX B

Personal Data

- Name
- Date of birth
- Email Address
- Residence Address
- Phone
- Citizenship information
- Residency information
- Race
- Gender
- Religion
- Health
- Financial information
- Purchasing history
- IP addresses
- Cookies

“data from which a living **individual** can be identified or identifiable (by anyone), whether directly or indirectly, by all means reasonably likely to be used”

Living Individual = Data Subject

APPENDIX C

Where and how do clients house personal data?

- Existing databases of customers, vendors, business contacts and others from contact forms

  - DMS
  - Email
  - Disaster Recovery Repositories
  - Communications with Government Agencies
  - Contact Management System
  - Billing System
  - Insurance carriers and brokers
  - Electronically Stored Information Systems
  - Phone System
  - Cookies
  - Tracker™
  - Docketing/Calendaring systems

- New Consent Forms from Data Subjects

- Payment (credit card, PayPal)

APPENDIX D

How should clients protect and safely share personal data?

- Passwords: the PD is kept in a password protected environment and is accessible only to those employees who must have access as part of their business function

- No Downloads: the PD should not be downloaded to a laptop, phone, thumb drive, or any other storage device and should not be printed unless it's necessary

- Safe Password Exchange: the passwords should be exchanged person to person, phone to phone (not voice mail) NOT BY email or text or voice mail

- Sharing: the document containing the PD should only be shared with specified third parties by authorized individuals

- Secure Hosted Environment: these services could be used for sharing the PD document (Dropbox, WeTransfer, etc.)

- Breach Notification: if the PD is breached, the client must notify the Data Subject within 72 hours of the client's knowledge of the breach; the client may wish to use a third party vendor

APPENDIX E

How do the data subjects access their personal data?

The client should implement a system to respond to a Data Subject's request to do any of the following:

- Update personal data
- Revoke permission to send marketing materials per each line item
- Object to the client's handling of personal data
- Instruct deletion of personal data but first confirm if the client has a legal obligation to maintain PD that in legal's view supersedes GDPR; health records must be maintained, for instance

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Helsinn v. Teva and Secret Prior Art

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Helsinn Healthcare S.A. v. Teva Pharmaceuticals Industries, Ltd.

What are secret sales and when are they considered prior art?

How license, distribution and other agreements between the patentee and third parties can raise issues with respect to issued patents and/or patent applications if the agreements are not properly drafted.

How the release of information to the public about agreements between the patentee and third parties can raise issues with respect to issued patents and/or patent applications.

Are there different criteria for whether a secret sale constitutes prior art depending on the filing date of the patent application, i.e., did the America Invents Act (AIA) change the definition of "on sale" for purposes of determining patentability?

When is a pharmaceutical invention "ready for patenting"?

Question for *Certiorari* Before the United States Supreme Court

Whether, under the Leahy-Smith America Invents Act, an inventor's sale of an invention to a third party that is obligated to keep the invention confidential qualifies as prior art for purposes of determining patentability of the invention.

Applicable Patent Statute

35 U.S.C. Sec. 102 - Conditions for Patentability (*pre AIA)*

A person shall be entitled to a patent unless …

the invention was patented or described in a printed publication in this or a foreign country or in public use or *on sale* in this country, more than one year prior to date of the application for patent in the United States (emphasis added)

35 U.S.C. Sec. 102 - Conditions for Patentability; Novelty *(current*)

A person shall be entitled to a patent unless …

the claimed invention was patented, described in a printed publication, or in public use, *on sale, or otherwise available to the public* before the effective filing date of the claimed invention (emphasis added)

United States Court of Appeals for the Federal Circuit

HELSINN HEALTHCARE S.A.,
Plaintiff-Appellee

v.

TEVA PHARMACEUTICALS USA, INC., TEVA PHARMACEUTICAL INDUSTRIES, LTD.,
Defendants-Appellants

2016-1284, 2016-1787

Appeals from the United States District Court for the District of New Jersey in Nos. 3:11-cv-03962-MLC-DEA, 3:11-cv-05579-MLC-DEA, 3:13-cv-05815-MLC-DEA, Judge Mary L. Cooper.

Decided: May 1, 2017

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Before DYK, MAYER, and O'MALLEY, *Circuit Judges*.

DYK, *Circuit Judge*.

Helsinn Healthcare S.A. ("Helsinn") is the owner of the four patents-in-suit directed to intravenous formulations of palonosetron for reducing or reducing the likelihood of chemotherapy-induced nausea and vomiting ("CINV").

Helsinn brought suit against Teva Pharmaceuticals USA, Inc. and Teva Pharmaceutical Industries, Ltd. (collectively, "Teva") alleging that the filing of Teva's Abbreviated New Drug Application ("ANDA") constituted an infringement of various claims of those patents. Teva defended, *inter alia*, on the ground that the asserted claims were invalid under the on-sale bar provision of 35 U.S.C. § 102. The district court found that the patents-in-suit were not invalid. With respect to three of the patents, which are governed by the pre-Leahy-Smith America Invents Act ("pre-AIA") version of § 102, the district court concluded that there was a commercial offer for sale before the critical date, but that the invention was not ready for patenting before the critical date. With respect to the fourth patent, which is governed by the AIA version of § 102, Pub. L. No. 112-29, § 3(b), 125 Stat. 284, 285–86 (2011), the district court concluded that there was no commercial offer for sale because the AIA changed the relevant standard and that, in any event, the invention was not ready for patenting before the critical date.

We reverse. The asserted claims of the patents-in-suit were subject to an invalidating contract for sale prior to the critical date of January 30, 2002, and the AIA did not change the statutory meaning of "on sale" in the circumstances involved here. The asserted claims were also ready for patenting prior to the critical date.

BACKGROUND

Helsinn owns four patents, U.S. Patent Nos. 7,947,724 ("'724 patent"), 7,947,725 ("'725 patent"), 7,960,424 ("'424 patent"), and 8,598,219 ("'219 patent") (collectively, "the patents-in-suit"), directed to reducing the likelihood of CINV. CINV is a serious side effect of chemotherapy treatment.

The use of palonosetron to treat CINV was not new. Indeed, U.S. Patent No. 5,202,333 ("'333 patent") taught that an intravenous formulation of palonosetron is "useful in the prevention and treatment of emesis," '333 patent, col. 9 ll. 56–57, including "emesis induced by . . . treatment for cancer with . . . chemotherapy," *id.* col. 10 ll. 7–9. The '333 patent is now expired. The patents-in-suit purport to disclose novel intravenous formulations using unexpectedly low concentrations of palonosetron that were not taught by the prior art. All four of the patents-in-suit claim priority to a provisional patent application filed on January 30, 2003. The critical date for the on-sale bar is one year earlier, January 30, 2002. The significance of the critical date is that a sale of the invention before that date can be invalidating.[1]

Helsinn alleged infringement of claims 2 and 9 of the '724 patent, claim 2 of the '725 patent, claim 6 of the '424 patent, and claims 1, 2, and 6 of the '219 patent (collectively, "the asserted claims"). Claim 2 of the '725 patent is representative of the asserted claims of the '724, '725, and '424 patents.

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[1] The parties agree that the '219 patent has the same critical date as the pre-AIA patents for the on-sale bar even though it is governed by the AIA. The one-year grace period in the AIA is less protective than under pre-AIA § 102(b) for reasons not relevant here.

> 2. A pharmaceutically stable solution for reducing emesis or reducing the likelihood of emesis comprising:
>
> a) 0.05 mg/mL palonosetron hydrochloride, based on the weight of the free base, in a sterile injectable aqueous carrier at a pH of from 4.5 to 5.5;
>
> b) from 0.005 mg/mL to 1.0 mg/mL EDTA; and
>
> c) mannitol in an amount sufficient to tonicify said solution, in a concentration of from about 10 mg/ml to about 80 mg/ml

'725 patent, col. 10 ll. 11–19.

Claim 1 is representative of the asserted claims of the '219 patent.

> 1. A pharmaceutical single-use, unit-dose formulation for intravenous administration to a human to reduce the likelihood of cancer chemotherapy-induced nausea and vomiting, comprising a 5 mL sterile aqueous isotonic solution, said solution comprising:
>
> palonosetron hydrochloride in an amount of 0.25 mg based on the weight of its free base;
>
> from 0.005 mg/mL to 1.0 mg/mL EDTA; and
>
> from 10 mg/mL to about 80 mg/mL mannitol,
>
> wherein said formulation is stable at 24 months when stored at room temperature.

'219 patent, col. 10 ll. 2–12. The claims of the patents-in-suit to some extent all express the same concepts in different terms. For instance, the '724, '725, and '424 patents claim a 0.05 mg/ml concentration of palonosetron, which equates to a total dose of 0.25 mg when administered in a 5 ml solution. The '219 patent expressly claims a fixed dose of 0.25 mg of palonosetron in a 5 ml solution. It is undisputed that each asserted claim covers the 0.25 mg dose of palonosetron. In order to simplify the relevant discussion, we refer to the patents as covering the 0.25 mg dose.

In 1998, Helsinn acquired a license under the '333 patent from Roche Palo Alto LLC ("Roche") to palonosetron and all intellectual property resulting from ongoing palonosetron research. Roche and its predecessor, Syntex (U.S.A.) Inc. ("Syntex"), had already conducted Phase I and Phase II clinical trials. A Phase II trial—Study 2330—found that the 0.25 mg dose "was effective in suppressing chemotherapy-induced emesis for 24 hours." J.A. 32, 1636. Helsinn then submitted safety and efficacy protocols for Phase III clinical trials to FDA in early 2000, proposing to study two dosages—0.25 mg and 0.75 mg. By early 2001 the Phase III trials were ongoing but not yet completed.

On April 6, 2001, almost two years before applying for a patent, Helsinn and MGI Pharma, Inc. ("MGI"), an oncology-focused pharmaceutical company that markets and distributes in the United States, entered into two agreements: (1) a License Agreement and (2) a Supply and Purchase Agreement. These agreements were announced in a joint press release of the two corporations and in MGI's Form 8-K filing with the Securities and Exchange Commission ("SEC"), which included partially-redacted copies of both agreements. *See* MGI Pharma Inc., Current Report (Form 8-K) Ex. 99.1 (Apr. 25, 2001) [hereinafter License Agreement]; MGI Pharma Inc., Current

Report (Form 8-K) Ex. 99.2 (Apr. 25, 2001) [hereinafter Supply and Purchase Agreement].

Under the terms of the License Agreement, MGI agreed to pay $11 million in initial payments to Helsinn, plus additional future royalties on distribution of "products" in the United States. The parties agree that the "products" covered by the License Agreement were 0.25 mg and 0.75 mg doses of palonosetron.

Under the Supply and Purchase Agreement, MGI agreed to purchase exclusively from Helsinn, and Helsinn agreed to supply MGI's requirements of the 0.25 mg and 0.75 mg palonosetron products, or whichever of the two dosages were approved for sale by FDA. The agreement required MGI to submit purchase forecasts to Helsinn and to place firm orders at least 90 days before delivery. It also specified that such orders would be "subject to written acceptance and confirmation by [Helsinn] before becoming binding." Supply and Purchase Agreement, *supra*, art. 4.2. But, in the event that Helsinn were unable to meet MGI's firm orders and to the extent they fell within the previously forecasted amount, Helsinn would then be obligated to designate a third party manufacturer to supply MGI with the product. The agreement specified price (29% of the gross sales price by MGI with a minimum of $28.50 per vial), method of payment (wire transfer within 30 days of receipt of an invoice), and method of delivery (DDU—which means delivery duty unpaid). *See* Black's Law Dictionary 481, 521 (10th ed. 2014) (defining "DDU" and "delivery duty unpaid").

The License Agreement made reference to the ongoing clinical trials and stated that in the event that the results were unfavorable and FDA did not approve the sale of either dosage of the product, Helsinn could terminate the agreement. If the License Agreement were terminated, the Supply and Purchase Agreement would "terminate

automatically." Supply and Purchase Agreement, *supra*, art. 11.1.

All of the above information about the transaction was publicly disclosed with two exceptions. The two features of the agreements that were not publicly disclosed were the price terms and the specific dosage formulations covered by the agreements—that is the 0.25 and 0.75 mg doses.

Helsinn admitted at oral argument that the agreement was binding as of its effective date, April 6, 2001, and that it would cover either or both of the 0.25 and 0.75 mg doses, subject to FDA approval. Helsinn also agreed that, if the Phase III trials were successful and the products were approved by FDA, then the agreement obligated MGI to purchase and Helsinn to supply the approved doses. But if FDA did not approve either dose, then the agreement likewise would terminate automatically with the License Agreement. As Helsinn stated, in such a scenario "both parties [could] accept that fact and walk away."[2] Oral Arg. at 36:37–40, http://oralarguments.cafc.uscourts.gov/default.aspx?fl=2016-1284.mp3.

After the signing of the agreements, and still before the critical date, Helsinn prepared preliminary statistical analysis of the earliest Phase III trial on January 7, 2002. The data showed that 81% of patients who received the 0.25 mg dose of palonosetron experienced relief from CINV for 24 hours. After the critical date of January 30,

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[2] Even if FDA approval were not an express condition of a contract for sale of a pharmaceutical, there would be a strong argument for implying such a condition since federal law prohibits the introduction of new drugs into interstate commerce without FDA approval. *See* 21 U.S.C. § 355.

2002, Helsinn submitted its preliminary Phase III data to FDA in early February. In September 2002, after the successful completion of all Phase III trials, Helsinn filed its New Drug Application for the 0.25 mg dose, but did not seek FDA approval of the 0.75 mg dose. On January 30, 2003, Helsinn filed a provisional patent application covering the 0.25 mg dose (and also the 0.75 mg dose). FDA issued approval for the 0.25 dose on July 2003. From 2005 to 2006, Helsinn filed three patent applications and these issued as the '724, '725, and '424 patents. In May 2013, after the effective date of the AIA, Helsinn filed a fourth patent application which issued as the '219 patent. All four patents cover the 0.25 mg dose, are listed in FDA's "Orange Book," and claim priority to the January 30, 2003 date of the provisional application.

In 2011, Teva filed an ANDA seeking FDA approval to market a generic 0.25 mg palonosetron product.[3] Teva's ANDA filing included a Paragraph IV certification that the claims of the patents-in-suit were invalid and/or not infringed. Helsinn then brought suit under the Hatch-

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[3] We treat this case as involving only the 0.25 mg dose of palonosetron. Teva also filed an ANDA for a 0.075 mg dose of palonosetron in 1.5 ml of solution. It is undisputed that this product has a concentration of 0.05 mg/ml and falls within the asserted claims of the '724, '725, and '424 patents. There is no contention that the 0.075 mg dose was on sale before the critical date or that the Supply and Purchase Agreement covered the 0.075 mg dose. But the parties agree that the same claims cover both the 0.25 mg dose and the 0.075 mg dose, and the case stands or falls on whether the asserted claims covering the 0.25 mg dose are invalid under the on-sale bar. In other words, if the claims covering the 0.25 mg dose are invalid, there are not valid and asserted claims covering the 0.075 mg dose.

Waxman Act, 35 U.S.C. § 271(e)(2)(A), alleging infringement of the patents-in-suit by the ANDA filing.

The district court held a bench trial. The district court held that Teva's 0.25 mg dose infringed all of the patents-in-suit. In addressing the on-sale issue, the court applied the two-step framework of *Pfaff v. Wells Electronics, Inc.*, 525 U.S. 55 (1998), which requires that there was a sale or offer for sale and that the claimed invention was ready for patenting for the on-sale bar under 35 U.S.C. § 102 to apply. As to the '724, '725, and '424 patents, the court found that pre-AIA law applied under § 102(b) and that the MGI Supply and Purchase Agreement was a contract for a future sale of a commercial product embodying the 0.25 mg dose and therefore constituted a sale under § 102(b). But, the court found that the claimed invention was not reduced to practice before the critical date of January 30, 2002, and therefore was not ready for patenting under the second prong of *Pfaff*. The district court did not address whether the invention was ready for patenting on the alternative theory that Teva had shown that the inventor had created enabling descriptions before the critical date. *See Pfaff*, 525 U.S. at 67–68.

As to the '219 patent governed by the AIA, the court held that the AIA changed the meaning of the on-sale bar and § 102(a)(1) now "requires a *public* sale or offer for sale of the claimed invention." J.A. 113 (emphasis added). The court concluded that, to be "public" under the AIA, a sale must publicly disclose the details of the invention. The court found that the MGI Supply and Purchase Agreement did not constitute a public sale or commercial offer for sale because, although it disclosed the sale agreement and substance of the transaction, it failed to publicly disclose the 0.25 mg dose. The '219 patent also was not ready for patenting before the critical date. Therefore, the district court found that the asserted claims of the four patents were not invalid.

Teva appeals. We have jurisdiction under 28 U.S.C. § 1295(a).

DISCUSSION

Application of the on-sale bar under 35 U.S.C. § 102 is ultimately a question of law that we review de novo. *Robotic Vision Sys., Inc. v. View Eng'g, Inc.*, 249 F.3d 1307, 1310 (Fed. Cir. 2001). The factual findings underlying the district court's conclusion are reviewed for clear error. *Id.* Under *Pfaff*, application of the on-sale bar requires that (1) "the product must be the subject of a commercial offer for sale" and (2) "the invention must be ready for patenting." 525 U.S. at 67.

I

We first address whether the invention of the '724, '725, and '424 patents was subject to a sale or offer for sale prior to the critical date. We recently had occasion to address the pre-AIA on-sale bar en banc in *Medicines Co. v. Hospira, Inc.*, 827 F.3d 1363 (Fed. Cir. 2016). There we established a framework for determining whether there is an offer for sale. We explained that the question must be "analyzed under the law of contracts as generally understood" and "must focus on those activities that would be understood to be commercial sales and offers for sale 'in the commercial community.'" *Id.* at 1373 (quoting *Grp. One, Ltd. v. Hallmark Cards, Inc.*, 254 F.3d 1041, 1047 (Fed. Cir. 2001)). While acknowledging that it is not of "talismanic significance" to our inquiry, "[a]s a general proposition, we will look to the Uniform Commercial Code ('UCC') to define whether . . . a communication or series of communications rises to the level of a commercial offer for sale." 827 F.3d at 1373 (alteration in original) (quoting *Grp. One*, 254 F.3d at 1047). A sale occurs when there is a "contract between parties to give and to pass rights of property for consideration which the buyer pays or promises to pay the seller for the thing bought or sold." *Trad-*

ing Techs. Int'l, Inc. v. eSpeed, Inc., 595 F.3d 1340, 1361 (Fed. Cir. 2010) (internal quotation marks omitted).

In *Medicines* we also pointed to other factors that are important to this analysis, but noted that, like the UCC itself, none is determinative individually. We noted that the absence of the passage of title, the confidential nature of a transaction, and the absence of commercial marketing of the invention all counsel against applying the on-sale bar. *Id.* at 1375–76. We deemed these factors important because they helped shed light on whether a transaction would be understood "in the commercial community" to constitute a commercial offer for sale. *Id.* at 1373 (quoting *Grp. One*, 254 F.3d at 1047). But those additional factors are not at issue in this case. There is no suggestion that the Supply and Purchase Agreement did not involve transfer of title; it expressly contemplated it. And, while certain details were redacted from the publicly disclosed copy of the Supply and Purchase Agreement, Helsinn does not argue that the *transaction* itself between Helsinn and MGI remained confidential. Helsinn also commercially marketed its invention before the critical date. It publicly sought "marketing partners for its patented [palonosetron] product," J.A. 63–64 n.26, and ultimately contracted with MGI "to distribute, promote, market, and sell" the claimed invention, J.A. 2255.

We agree with the district court that there was a sale for purposes of pre-AIA § 102(b) prior to the critical date because there was a sale of the invention under the law of contracts as generally understood.

Helsinn admits that the Supply and Purchase Agreement was binding as of its effective date, April 6, 2001, and that, if FDA approved the 0.25 mg dose and/or the 0.75 mg dose of palonosetron, the agreement obligated Helsinn to sell and MGI to purchase those products. The

Supply and Purchase Agreement bears all the hallmarks of a commercial contract for sale.[4] It obligated MGI to purchase exclusively from Helsinn and obligated Helsinn to supply MGI's requirements of the 0.25 and 0.75 mg doses if approved by FDA.

The agreement here included other specific terms, such as price, method of payment, and method of delivery. Even though MGI's firm orders pursuant to the agreement were ostensibly "subject to written acceptance and confirmation by [Helsinn] before becoming binding," J.A. 2260, Helsinn was nonetheless obligated to meet or designate a third party manufacturer to meet MGI's firm orders. The public 8-K filing described the Supply and Purchase Agreement as obligating Helsinn to supply MGI's "requirements of finished product." MGI Pharma Inc., Current Report (Form 8-K), at 2 (Apr. 25, 2001). Under our decision in *Enzo Biochem, Inc. v. Gen-Probe, Inc.*, 424 F.3d 1276 (Fed. Cir. 2005), the fact that an agreement covered one party's requirements as opposed to a specified quantity does not prevent application of the on-sale bar. *Id.* at 1281–82.

Despite these facts, Helsinn argues that the Supply and Purchase Agreement is not invalidating because at the critical date it was uncertain whether FDA would

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[4] *See, e.g.*, *Merck & Cie v. Watson Labs., Inc.*, 822 F.3d 1347, 1351 (Fed. Cir. 2016) (offer "provid[ed] essential price, delivery, and payment terms"); *Cargill, Inc. v. Canbra Foods, Ltd.*, 476 F.3d 1359, 1369 (Fed. Cir. 2007) (offer "explicitly set[] forth an amount . . . to be delivered to P&G, at a specified unit price, and under a standard contract designation, FOB (free on board)"); *Linear Tech. Corp. v. Micrel, Inc.*, 275 F.3d 1040, 1052 (Fed. Cir. 2001) (offers "included quantity terms and clearly identified the requested product").

approve the 0.25 mg dose, and FDA approval was a condition precedent to the sale.

There can be no real dispute that an agreement contracting for the sale of the claimed invention contingent on regulatory approval is still a commercial sale as the commercial community would understand that term. The UCC expressly provides that a "purported present sale of future goods . . . operates as a contract to sell." UCC § 2–105(2) (defining "future goods" as "[g]oods which are not both existing and identified"). This is true irrespective of whether those future goods have yet to receive necessary regulatory approval. A contract for sale that includes a condition precedent is a valid and enforceable contract. *See BG Grp., PLC v. Republic of Argentina*, 134 S. Ct. 1198, 1207 (2014). Indeed, conditions precedent such as regulatory approval are a basic feature of contract law.[5] *See, e.g.*, 25 Williston on Contracts § 67:73, at 462 (4th ed. 2013) ("Particular construction or development projects may also require specific governmental or regulatory approvals as conditions precedent to the consummation of the project."); 8 Corbin on Contracts § 31.11, at 99–101 (1999) ("In many contracts it is expressly provided that some act of a third person shall be a condition of a promisor's duty . . . [such as a duty] to buy property contingent on a zoning board's approval . . . .").

It has been implicit in our prior opinions that the absence of FDA or other regulatory approval before the

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[5] "A condition precedent is either an act of a party that must be performed or a certain event that must happen before a contractual right accrues or a contractual duty arises." 13 Williston on Contracts § 38:7, at 434–37 (4th ed. 2013); *see also id.* § 38:7, at 434–46; Restatement (Second) of Contracts § 224 (1981); 2 Anderson U.C.C. § 2-301:11, at 149–52 (3d. ed. 2013); 8 Corbin on Contracts §§ 30.6–30.7, at 9–15 (1999).

critical date does not prevent a sale or offer for sale from triggering the on-sale bar. For instance, in *Enzo*, we applied the on-sale bar even though the contract for sale covered the buyer's reasonable requirements for "*perform[ing] all preclinical and clinical studies*," by definition before FDA approval, because the "claimed invention, the polynucleotide probe, is a tangible item or product that can be sold or offered for sale." 424 F.3d at 1279, 1282 (emphasis added). Similarly, in *C.R. Bard, Inc. v. M3 Sys., Inc.*, 157 F.3d 1340 (Fed. Cir. 1998), we affirmed a jury verdict of invalidity based on a sale even though the product sold was subject to regulatory approval. There was no majority opinion, but through two separate individual opinions a majority of the panel held that the on-sale bar applied. *Id.* at 1354 n.4. One opinion explicitly addressed the patentee's argument that the offer to sell did not trigger the statutory bar because "FDA approval had not been obtained" before the critical date, concluding that "FDA approval is not required before a sale can bar patent rights." *Id.* at 1376 (Mayer, C.J.). The dissent recognized that the majority was rejecting the argument that the product was not on sale because at the time of the sale it was "still being developed [and] tested" for FDA approval. *Id.* at 1357 (Newman, J.). Thus, while the absence of FDA approval may be a relevant consideration depending upon the other circumstances surrounding a transaction relating to a pharmaceutical formulation, the fact that a transaction was subject to regulatory approval would not, absent more, prevent it from being a sale for purposes of the on-sale bar. We do not find that it does so here. This is not a case like *Elan Corp., PLC v. Andrx Pharm., Inc.*, 366 F.3d 1336 (Fed. Cir. 2004), where the purported offer concerned a product when and if it had been developed, and there was no price or quantity term. *Id.* at 1341.

Helsinn also argues that, even if the agreement of sale for the 0.25 mg dose could be an invalidating sale, the

agreement was uncertain because it covered the 0.25 mg dose, the 0.75 mg dose, and both doses. Helsinn is correct that the agreement covered either dose or both doses. Under established contract law, even if the agreement had given MGI, as the purchaser, the option of choosing between the two doses, as opposed to making the decision dependent on actions of third party regulators, there would still be a binding agreement.[6]

In any event, here there is no ambiguity introduced by the provision for the purchase of either or both doses. This contract is indistinguishable from a situation involving two otherwise identical contracts, one covering the 0.25 mg dose and the other covering the 0.75 mg dose, each contingent on FDA approval. It is clear that these two hypothetical agreements would individually trigger the on-sale bar for the 0.25 mg dose and the 0.75 mg dose, respectively. It cannot be that combining them into a single agreement somehow thwarts application of the on-sale bar. We see no valid reason based in contract law, patent law, or otherwise, to distinguish between a single agreement that covers two potential products—like the one between Helsinn and MGI—and two separate agreements, one for each product.

Our en banc decision in *Medicines* also made clear that the offer or contract for sale must unambiguously place *the invention* on sale, as defined by the patent's claims. 827 F.3d at 1374. As discussed below, that is clearly the case here. The Supply and Purchase Agree-

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[6] *See, e.g.*, 1 Corbin on Contracts § 4.6 (citing *Dolly Parker Motors, Inc. v. Stinson*, 245 S.W.2d 820 (Ark. 1952); *Delaney v. Shellabarger*, 353 P.2d 903 (Nev. 1960); *Langer v. Lemke*, 49 N.W.2d 641 (N.D. 1951); *Calder v. Third Judicial Dist. Court*, 273 P.2d 168 (Utah 1954)); *C.W. Hull Co. v. Westerfield*, 186 N.W. 992, 994 (Neb. 1922).

ment described the palonosetron formulation in detail and Helsinn does not assert that the 0.25 mg dose described in the Supply and Purchase Agreement does not embody the asserted claims of the patents-in-suit. The fact that the contract made the selection of which doses to supply contingent on regulatory approval did not create an ambiguity with respect to whether what was on sale fell within the bounds of the patents' claims.

At oral argument for the first time, Helsinn contended that applying the on-sale bar would be unfair because it would distinguish between vertically-integrated manufacturers that have in-house distribution capacity and smaller entities like Helsinn that must contract for distribution services from a third party. Helsinn asserts that *Medicines* stands for the proposition that we should not allow commercial activities to be invalidating if those same activities could be performed in-house without triggering the on-sale bar. Such a broad principle would largely eviscerate the on-sale bar provision except as to sales to end users; that was not the holding of *Medicines*. There we concluded that "stockpiling," including purchases from a supplier, "does not trigger the on-sale bar." 827 F.3d at 1374. We also expressed concern over a policy of "penalizing a company for relying, by choice or by necessity, on the confidential services of a contract manufacturer." *Id.* at 1378. But the concern that *Medicines* focused on is not applicable here. Helsinn did not contract for MGI's confidential marketing or distribution services as Medicines contracted for Ben Venue's confidential manufacturing services. Instead, the Supply and Purchase Agreement between Helsinn and MGI unambiguously contemplated the sale by Helsinn of MGI's requirements of the claimed invention.

It is clear that the Supply and Purchase Agreement constituted a commercial sale or offer for sale for purposes of § 102(b) as to the asserted claims of the '724, '725, and '424 patents.

II

We next address whether the AIA changed the meaning of the on-sale bar under 35 U.S.C. § 102 so that there was no qualifying sale as to the '219 patent. The parties agree that the '219 patent is governed by the AIA. *See* 35 U.S.C. § 102(a)(1); AIA, Pub. L. No. 112-29, § 3(n), 125 Stat. 284, 293 (2011).

Before the AIA, § 102(b) barred the patentability of an invention that was "patented or described in a printed publication in this or a foreign country or in public use or *on sale* in this country, more than one year prior to the date of the application for patent." 35 U.S.C. § 102(b) (2006) (emphasis added). Under that earlier provision, we concluded that, although confidentiality weighs against application of the on-sale bar, *see Medicines*, 827 F.3d at 1376, 1377 n.2, that fact alone is not determinative.[7] For

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[7] *See, e.g.*, *Woodland Trust v. Flowertree Nursery, Inc.*, 148 F.3d 1368, 1370 (Fed. Cir. 1998) (stating that "an inventor's own prior commercial use, albeit kept secret, may constitute a public use or sale under § 102(b), barring him from obtaining a patent"); *J.A. LaPorte, Inc. v. Norfolk Dredging Co.*, 787 F.2d 1577, 1581–83 (Fed. Cir. 1986) (stating that the on-sale bar "is not limited to sales by the inventor or one under his control, but may result from activities of a third party" and rejecting the argument that "secret commercialization by a third party" is not invalidating since "the invention . . . was discoverable from the device which was sold" and the "device . . . embodie[d] the invention" (emphasis omitted)); *In re Caveney*, 761 F.2d 671, 675 (Fed. Cir. 1985) (rejecting the argument that a secret sale by a third party was not invalidating because "sales or offers by one person of a claimed invention will bar another party from obtaining a patent"); *see also* 2 R. Carl Moy, Moy's Walker on Patents § 8:228 (4th ed. 2016) ("[E]ven a private sale or offer for

instance, in *In re Caveney*, a British company offered to sell the claimed invention to an American company that would be its exclusive seller in the United States before the critical date. *In re Caveney*, 761 F.2d 671, 673–74 (Fed. Cir. 1985). The court rejected the argument that a sale or offer for sale did not trigger the on-sale bar when it had been "kept secret from the trade," concluding that "sales or offers by one person of a claimed invention . . . bar another party from obtaining a patent if the sale or offer to sell is made over a year before the latter's filing date." *Id.* at 675.

By enacting the AIA, Congress amended § 102 to bar the patentability of an "invention [that] was patented, described in a printed publication, or in public use, *on sale*, or otherwise available to the public before the effective filing date of the claimed invention." 35 U.S.C. § 102(a)(1) (emphasis added).

Teva and various amici assert that by reenacting the existing statutory term, "on sale," Congress did not change the meaning of the on-sale bar or disturb settled law. Helsinn, the government, and other amici argue that the AIA changed the law by adding the "otherwise available to the public" phrase. They argue that the on-sale bar now does not encompass secret sales and requires that a sale make the invention available to the public in order to trigger application of the on-sale bar. Apart from the additional statutory language, this argument primarily relies on floor statements made by individual members of Congress. While recognizing that such floor statements are typically not reliable as indicators of congressional intent, *see, e.g.*, *Exxon Mobil Corp. v. Allapattah Servs.,*

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sale can be a barring event."); 3 John Gladstone Mills III et al., Pat. L. Fundamentals § 10:12 (2d ed. 2017) ("An invention is 'on sale' even though the only sale was a 'private' one.").

Inc., 545 U.S. 546, 568 (2005), they argue that here we should look to the floor statements to determine the meaning of the provision. These floor statements include material such as the following:

> [S]ubsection 102(a) was drafted in part to do away with precedent under current law that *private offers for sale* or private uses or secret processes practiced in the United States that result in a product or service that is then made public may be deemed patent-defeating prior art. That will no longer be the case.

157 Cong. Rec. 3415 (2011) (remarks of Sen. Leahy) (emphasis added).

> [T]he current on-sale bar imposes penalties not demanded by any legitimate public interest. There is no reason to fear 'commercialization' that merely consists of a *secret sale or offer for sale* but that does not operate to disclose the invention to the public. . . . The present bill's new section 102(a) precludes extreme results such as these . . . .

157 Cong. Rec. 3424 (2011) (remarks of Sen. Kyl) (emphasis added).[8]

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[8] *See also* 157 Cong. Rec. 3423 (2011) (remarks of Sen. Kyl) ("The word 'otherwise' makes clear that the preceding clauses describe things that are of the same quality or nature . . . . As the committee report notes at page 9, 'the phrase "available to the public" is added to clarify the broad scope of relevant prior art, as well as to emphasize the fact that it . . . must be publicly available.'"); 157 Cong. Rec. 9782 (2011) (remarks of Sen. Smith) ("[C]ontrary to current precedent, in order to trigger the bar in the new 102(a) in our legislation, an action must

We decline the invitation by the parties to decide this case more broadly than necessary. At most the floor statements show an intent "to do away with precedent under current [§ 102] law," 157 Cong. Rec. 3415 (2011) (remarks of Sen. Leahy). Such precedent had held certain secret uses to be invalidating under the "public use" prong of § 102(b). Senator Kyl explicitly referenced cases such as *Egbert v. Lippman*, 104 U.S. 333 (1881), *Beachcombers International, Inc. v. Wildewood Creative Products, Inc.*, 31 F.3d 1154 (Fed. Cir. 1994), and *JumpSport, Inc. v. Jumpking, Inc.*, Nos. 05–1182, 05–1196, 05–1197, 2006 WL 2034498 (Fed. Cir. July 21, 2006), and stated that "new section 102(a) precludes extreme results such as these." 157 Cong. Rec. 3424 (2011) (remarks of Sen. Kyl). Each of those cases involved a public use where the invention was not, as a result of the use, disclosed to the public. This public use issue is not before us, and we decline to address it.

The floor statements do not identify any *sale* cases that would be overturned by the amendments. Even if the floor statements were intended to overrule those secret or confidential sale cases discussed above and cited in footnote 7, that would have no effect here since those cases were concerned entirely with whether the existence of a sale or offer was public. Here, the existence of the sale—*i.e.*, the Supply and Purchase Agreement between Helsinn and MGI—was publicly announced in MGI's 8-K filing with the SEC. The 8-K filing also included a copy of the contract for sale as an attachment, albeit partially redacted. Detailed information about palonosetron, its benefits and uses in treating CINV were also disclosed. The statements disclosed the chemical structure of palonosetron and specified that the covered products were

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make the patented subject matter 'available to the public' before the effective filing date.").

"pharmaceutical preparations for human use in [intravenous] dosage form, containing [palonosetron] as an active ingredient." Supply and Purchase Agreement, *supra*, art. 1.9.[9] And, as described above, the agreements disclosed all the pertinent details of the transaction other than the price and dosage levels.

Helsinn argues that the AIA did more than overrule the "secret sale" cases, and relies on the "otherwise available to the public" language in the statute and the floor statements. Helsinn argues that those statements suggest that the on-sale bar does not apply unless the sale "disclose[s] the invention to the public" before the critical date. 157 Cong. Rec. 3424 (2011) (remarks of Sen. Kyl). It urges that since the 0.25 mg dose was not disclosed, the invention was not disclosed and the on-sale bar does not apply. The suggestion is that Congress required that the details of the claimed invention be publicly disclosed before the on-sale bar is triggered.

Requiring such disclosure as a condition of the on-sale bar would work a foundational change in the theory of the statutory on-sale bar. Indeed, the seminal Supreme Court

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[9] The joint April 10, 2001 press release stated that "[p]alonosetron is a potent and selective 5-HT3 antagonist with an extended half-life, in Phase 3 development for the prevention of chemotherapy-induced nausea and vomiting (CINV)." MGI Pharma Inc., Current Report (Form 8-K) Ex. 99.5, at 1 (Apr. 25, 2001). It also disclosed that, once launched, it would "be one of four products competing in the $1 billion North American market for 5-HT3 antagonists . . . [and its] extended half-life . . . as compared to the other agents and the results of Phase 2 trials assessing efficacy beyond 24 hours differentiate[] palonosetron from the three currently marketed 5-HT3 antagonists indicated for CINV." *Id.* at 2.

decision in *Pennock* addressed exactly such a situation[10]—the public sale of an item but the withholding from "the public the secrets of [the] invention." *Pennock v. Dialogue*, 27 U.S. (2 Pet.) 1, 19 (1829). Failing to find such a sale invalidating, said the Court, "would materially retard the progress of science and the useful arts, and give a premium to those who should be least prompt to communicate their discoveries." *Id.*

So too under our cases, an invention is made available to the public when there is a commercial offer or contract to sell a product embodying the invention and that sale is made public. Our cases explicitly rejected a requirement that the details of the invention be disclosed in the terms of sale. *See RCA Corp. v. Data Gen. Corp.*, 887 F.2d 1056, 1060 (Fed. Cir. 1989), *overruled in part on other grounds by Grp. One*, 254 F.3d at 1048 (rejecting the argument "that the bid documents themselves must disclose the invention with respect to all claim elements" since that is "clearly not legally correct" and there can be "a definite

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[10] *Pennock v. Dialogue*, 27 U.S. (2 Pet.) 1, 19 (1829) ("If an inventor should be permitted to hold back from the knowledge of the public the secrets of his invention; if he should for a long period of years retain the monopoly, and make, and sell his invention publicly, and thus gather the whole profits of it, relying upon his superior skill and knowledge of the structure; and then, and then only, when the danger of competition should force him to secure the exclusive right, he should be allowed to take out a patent, and thus exclude the public from any farther use than what should be derived under it during his fourteen years; it would materially retard the progress of science and the useful arts, and give a premium to those who should be least prompt to communicate their discoveries.").

offer for sale or a sale of a claimed invention even though *no* details are disclosed").

A primary rationale of the on-sale bar is that publicly offering a product for sale that embodies the claimed invention places it in the public domain, regardless of when or whether actual delivery occurs.[11] The patented product need not be on-hand or even delivered prior to the critical date to trigger the on-sale bar.[12] And, as previous-

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[11] *See, e.g.*, *Pfaff*, 525 U.S. at 64 ("§ 102 of the Patent Act serves as a limiting provision, both excluding ideas that are in the public domain from patent protection and confining the duration of the monopoly to the statutory term. . . . A similar reluctance to allow an inventor to remove existing knowledge from public use undergirds the on-sale bar."); *Merck & Cie*, 822 F.3d at 1355 n.4 ("One of the primary purposes of the on-sale bar is to prohibit the withdrawal of inventions that have been placed into the public domain through commercialization." (internal quotation marks omitted) (quoting *Abbott Labs. v. Geneva Pharm., Inc.*, 182 F.3d 1315, 1319 (Fed. Cir. 1999))); *J.A. LaPorte*, 787 F.2d at 1583 ("The date of the purchase agreement is, therefore, the effective date on which the invention became part of the public domain. That delivery of the device embodying the invention occurred later is immaterial.").

[12] *See, e.g.*, *Pfaff*, 525 U.S. at 58, 67 (applying the on-sale bar where the sale order was not filled until after the critical date); *STX, LLC v. Brine, Inc.*, 211 F.3d 588, 590 (Fed. Cir. 2000) (same); *Buildex Inc. v. Kason Indus., Inc.*, 849 F.2d 1461, 1464 (Fed. Cir. 1988) ("Proof of delivery before the critical date would have been conclusive in this case, but it is not necessary to holding that the device was on sale before then."); *Robbins Co. v. Lawrence Mfg. Co.*, 482 F.2d 426, 431 (9th Cir. 1973) ("A simple placing on sale is sufficient to establish the 'on sale' defense—even

ly noted, we have never required that a sale be consummated or an offer accepted for the invention to be in the public domain and the on-sale bar to apply, nor have we distinguished sales from mere offers for sale.[13] We have also not required that members of the public be aware that the product sold actually embodies the claimed invention. For instance, in *Abbott Laboratories v. Geneva Pharmaceuticals, Inc.*, 182 F.3d 1315 (Fed. Cir. 1999), at the time of the sale, neither party to the transaction knew

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an executory contract under which the patented matter is delivered after the critical date.").

[13] *See, e.g.*, *Pfaff*, 525 U.S. at 67 ("[A]cceptance of the purchase order prior to April 8, 1981, makes it clear that . . . an offer had been made."); *Merck & Cie*, 822 F.3d at 1352 ("An offer to sell is sufficient to raise the on-sale bar, regardless of whether that sale is ever consummated."); *Hamilton Beach Brands, Inc. v. Sunbeam Prods., Inc.*, 726 F.3d 1370, 1374, 1377 (Fed. Cir. 2013) ("An actual sale is not required for the activity to be an invalidating commercial offer for sale."); *Cargill*, 476 F.3d at 1370 ("There is no requirement that the sale be completed."); *Scaltech, Inc. v. Retec/Tetra, LLC*, 269 F.3d 1321, 1328 (Fed. Cir. 2001) ("An offer for sale does not have to be accepted to implicate the on sale bar."); *A.B. Chance Co. v. RTE Corp.*, 854 F.2d 1307, 1311 (Fed. Cir. 1988) ("A single offer to sell is enough to bar patentability whether or not the offer is accepted."); *Buildex*, 849 F.2d at 1464 ("It is not necessary that a sale be consummated for the bar to operate."); *In re Theis*, 610 F.2d 786, 791 (CCPA 1979) ("For § 102(b) to apply, it is not necessary that a sale be consummated."); *Mfg. Research Corp. v. Graybar Elec. Co.*, 679 F.2d 1355, 1362 (11th Cir. 1982) ("The statutory on sale bar applies when the invention that is the subject of a patent application is merely offered for sale; there is no requirement that a sale be consummated before the statutory bar attaches.").

whether the product sold embodied the claimed invention and had no easy way to determine what the product was. *Id.* at 1317–18.

Thus, our prior cases have applied the on-sale bar even when there is no delivery, when delivery is set after the critical date, or, even when, upon delivery, members of the public could not ascertain the claimed invention. There is no indication in the floor statements that these members intended to overrule these cases. In stating that the invention must be available to the public they evidently meant that the public sale itself would put the patented product in the hands of the public. Senator Kyl himself seems to have agreed with this proposition, stating explicitly that "once a product is sold on the market, any invention that is inherent to the product becomes publicly available prior art and cannot be patented." 157 Cong. Rec. 3423 (2011) (remarks of Sen. Kyl).[14] There are no floor statements suggesting that the sale or offer documents must themselves publicly disclose the details of the claimed invention before the critical date. If Congress intended to work such a sweeping change to our on-sale bar jurisprudence and "wished to repeal . . . [these prior] cases legislatively, it would do so by clear language." *Dir., OWCP v. Perini N. River Assocs.*, 459 U.S. 297, 321 (1983).

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[14] Senator Kyl quoted our anticipation decision in *Rosco, Inc. v. Mirror Lite Co.*, 304 F.3d 1373 (Fed. Cir. 2002). "Under the doctrine of inherency, if an element is not expressly disclosed in a prior art reference, the reference will still be deemed to anticipate a subsequent claim if the missing element is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill." 157 Cong. Rec. 3423 (2011) (remarks of Sen. Kyl) (internal quotation marks omitted) (quoting *Rosco*, 304 F.3d at 1380).

We conclude that, after the AIA, if the existence of the sale is public, the details of the invention need not be publicly disclosed in the terms of sale. For the reasons already stated, the Supply and Purchase Agreement between Helsinn and MGI constituted a sale of the claimed invention—the 0.25 mg dose—before the critical date, and therefore both the pre-AIA and AIA on-sale bars apply. We do not find that distribution agreements will always be invalidating under § 102(b). We simply find that this particular Supply and Purchase Agreement is.

III

We finally address whether the invention was ready for patenting as of the critical date of January 30, 2002. Under *Pfaff*, there are at least two ways in which an invention can be shown to be ready for patenting: "by proof of reduction to practice before the critical date; or by proof that prior to the critical date the inventor had prepared drawings or other descriptions of the invention that were sufficiently specific to enable a person skilled in the art to practice the invention." *Pfaff*, 525 U.S. at 67–68. We conclude that the invention here was ready for patenting because it was reduced to practice before the critical date, and we need not address the alternative enablement approach, not addressed by the district court.[15]

A. Reduction to Practice

An invention is reduced to practice when "the inventor (1) constructed an embodiment . . . that met all the limitations and (2) determined that the invention would work for its intended purpose." *In re Omeprazole Patent Litig.*, 536 F.3d 1361, 1373 (Fed. Cir. 2008) (internal quotation marks and citations omitted) (citing *Z4 Techs., Inc. v. Microsoft Corp.*, 507 F.3d 1340, 1352 (Fed. Cir. 2007)). Reduction to practice occurs if "the claimant had

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[15] *See* J.A. 130 n.53.

possession of the subject matter of the [claim] and that it was shown or known to work for its intended purpose."[16] *Streck, Inc. v. Research & Diagnostic Sys., Inc.*, 659 F.3d 1186, 1193 (Fed. Cir. 2011); *accord Sanofi-Aventis v. Pfizer Inc.*, 733 F.3d 1364, 1367–68 (Fed. Cir. 2013).

Before trial, the parties stipulated that they would contest ready for patenting "only with respect to the limitations and intended uses of 'reducing emesis or reducing the likelihood of emesis' and 'to reduce the likelihood of cancer chemotherapy-induced nausea and vomiting' of the asserted claims" and not "for any other reason." J.A. 26081. Thus, for instance, it is uncontested that the formulation had been made and was stable prior to the critical date. Accordingly, the only issue with respect to ready for patenting before the district court and on appeal is whether Helsinn had determined that the invention would work for its intended purpose, which, according to the claims, is "reducing the likelihood" of emesis and CINV.

Our cases distinguish between the standard required to show that a particular invention would work for its intended purpose and the standard that governs FDA approval of new drugs, including the various stages of clinical trials. *See, e.g.*, *Scott v. Finney*, 34 F.3d 1058, 1063–64 (Fed. Cir. 1994) (addressing reduction to practice in the priority context). In patent law, the requisite testing, if any, for showing that an invention will "work for its intended purpose" varies depending on "the character of the invention," including the claim language and the

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[16] *See, e.g.*, *Honeywell Int'l Inc. v. Universal Avionics Sys. Corp.*, 488 F.3d 982, 997 (Fed. Cir. 2007) (citing to *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1563 (Fed. Cir. 1996), a case that addresses ready for patenting in the priority context, for the ready for patenting standard in the context of the on-sale bar).

"nature and complexity of the problem" the invention seeks to solve. *Id.* at 1061–62; *see also Slip Track Sys., Inc. v. Metal-Lite, Inc.*, 304 F.3d 1256, 1265 (Fed. Cir. 2002). Generally there must be some "demonstration of the workability or utility of the claimed invention." *Honeywell Int'l Inc. v. Universal Avionics Sys. Corp.*, 488 F.3d 982, 997 (Fed. Cir. 2007). This must show that the invention works for its intended purpose "beyond a probability of failure" but not "beyond a possibility of failure." *Scott*, 34 F.3d at 1062. "[L]ater refinements do not preclude reduction to practice, [and] it is improper to conclude that an invention is not reduced to practice merely because further testing is being conducted." *Atlanta Attachment Co. v. Leggett & Platt, Inc.*, 516 F.3d 1361, 1367 (Fed. Cir. 2008).

Approval of a new drug by FDA, however, is a more demanding standard than that involved in the patents-in-suit. The patents here make no reference to FDA standards and broadly claim a palonosetron formulation for reducing the likelihood of emesis and CINV. For FDA approval, however, an applicant must submit, *inter alia*, "adequate tests by all methods reasonably applicable to show whether or not such drug is safe for use" and "substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed." 21 U.S.C. § 355(d). This requires "adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof." *Id.* This is understood to be "a rigorous standard." *Ams. for Safe Access v. DEA*, 706 F.3d 438, 451 (D.C. Cir. 2013).

Here, the district court based its finding that the invention was not reduced to practice before the critical date on insufficient testing for Helsinn to have "determined that the invention would work for its intended purpose." J.A. 159. The district court appeared to believe that Teva needed to meet the FDA standard, which requires finalized reports with fully analyzed results from successful Phase III trials. This is clear from the district court's reliance on the testimony of Helsinn's expert who "referred to FDA standards in forming his opinions in this case" and stated that FDA "articulated a statistical framework for being able to really know from the [clinical trial] data . . . that a drug is working." J.A. 148. Throughout its opinion the district court found lack of reduction to practice for failure to establish "efficacy" under FDA standards, and the lack of fully analyzed Phase III studies as required by FDA. J.A. 159. The district court was influenced particularly by the fact that FDA found the so-called Study 2330 insufficient to demonstrate efficacy.[17] *See, e.g.*, J.A. 34, 48–50, 56, 147, 151, 154–55.

The district court clearly erred by applying too demanding a standard. The completion of Phase III studies and final FDA approval are not pre-requisites for the invention here to be ready for patenting. The evidence is overwhelming that before the critical date of January 30, 2002, it was established that the patented invention would work for its intended purpose of reducing the likelihood of emesis.

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[17] FDA found Study 2330 insufficient on its own to support Phase III trials since, "[w]hen compared to the lowest doses (0.3 and 1 mcg/kg) only the 30 mcg/kg dose was statistically significant; a significant dose response trend was not evident." J.A. 10907. We view this as irrelevant to whether the invention was ready for patenting.

- The 1995 report from Study 2330 demonstrated that three different doses, including the 0.25 mg dose, produced statistically significant results at the 5% level for the median time it took patients to experience an emetic episode after administration of palonosetron. While this study did not show statistical significance for complete control of emesis or CINV for 24 hours, complete control is not a claim requirement. The invention is for reducing the likelihood of emesis, not necessarily completely preventing it, and the statistical significance for mean time to failure demonstrates that the product reduced the likelihood of emesis. Indeed, the Study 2330 final report concluded that the relevant dose of palonosetron "was effective in suppressing" CINV. J.A. 1636. Under our cases this is sufficient to establish that the invention here would work for its intended purpose of reducing the likelihood of CINV. *See, e.g.*, *Z4 Techs.*, 507 F.3d at 1352 (concluding that the intended purpose of the invention at issue was to reduce piracy, not to completely stop its occurrence).
- Giorgio Calderari, one of the named inventors of the patents-in-suit, characterized the results of the Phase II trial, Study 2330, as "yes, the product was showing some efficacy clearly." J.A. 524.
- Minutes from a July 1998 meeting of Helsinn's palonosetron team indicated that their "proposal [wa]s to test *effective* doses seen in Phase 2," including the 0.25 mg dose. J.A. 1424 (emphasis added).
- The proposed protocols for Phase III trials that Helsinn submitted to FDA in November 1999

stated that the "[r]esults achieved in Phase II CINV studies suggest that palonosetron is safe and effective in preventing nausea and vomiting following emetogenic chemotherapy," J.A. 3846, and "[d]ata from this study clearly demonstrate that the 3 μg/kg dose of palonosetron is the minimal effective dose in preventing CINV," J.A. 3851.

- On September 14, 2000, Helsinn announced in a press release that "Phase II trials [had] demonstrated the efficacy of Palonosetron in the prevention of emesis with no significant side effects." J.A. 9983.
- On January 7, 2002, Helsinn prepared preliminary data tables analyzing the results from the first Phase III trial.[18] "[T]he preliminary data for Complete Response, which is the primary efficacy outcome measure for acute CINV, was 81.0% (153/189) for palonosetron 0.25 mg." J.A. 81. This means that 81% of patients who received the 0.25 mg dose of palonosetron experienced relief from CINV for 24 hours. As one of the named inventors of all four patents explained, these data showed that the 0.25 mg dose of palonosetron "reduced the likelihood of CINV in those subjects." J.A. 593.

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[18] Even though the purported sale or offer for sale occurred before these data tables were prepared, post-contract developments are relevant such that even if an invention is not ready for patenting at the time of the offer or sale, it may become so before the critical date and thereby trigger application of the on-sale bar, a point to which both parties agreed at oral argument.

- In a 2007 declaration submitted to overcome an initial rejection by the examiner during prosecution, Giorgio Calderari and four of the other named inventors of the patents-in-suit stated that "[t]he formulations . . . were completed sometime before March 24, 1999" and that they "had invented and were in possession of all of the subject matter currently claimed . . . as of March 24, 1999." J.A. 1411–12. This was clarified at trial as referring to the claimed invention, *i.e.*, "a pharmaceutically stable solution for reducing emesis or reducing the likelihood of emesis." J.A. 527 (154:16–22; 156:1–9).
- In a 2010 declaration corresponding to another related palonosetron patent application,[19] Sergio Cantoreggi and two named inventors of the '724, '725, and '424 patents submitted a declaration stating that they "had conceived the invention . . . , and reduced it to practice, before November 16, 2001," J.A. 2921 ¶ 2, and "had conceived the idea to use palonosetron for the treatment of acute and delayed-onset CINV, and had conducted clinical trials in humans to test this idea, at least as early as October 2, 2001," J.A. 2921 ¶ 3. The declaration concluded

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[19] The patent application claimed a method of treating CINV with the 0.25 mg dose: "A method of treating chemotherapy or radiotherapy-induced acute and delayed emesis in an adult human for five days after an emesis inducing chemotherapy or radiotherapy event, comprising administering to said human a single dose of a treatment-effective amount of about 0.25 mg of palonosetron in the form of palonosetron hydrochloride prior to said emesis-inducing event, without administering any further palonosetron during said give day period." J.A. 2922.

> that "[m]ost important, [they] had successfully tested the method in human patients, and [they] had done so before October 2, 2001 (the date the [Phase III] study was completed)." J.A. 2923 ¶ 18. The district court found that these statements in the 2010 declaration "were literally true." J.A. 158.

These results consistently showed that the invention worked for its intended purpose, from the final report for the 1995 Phase II trial to the preliminary results in January 2002 from a Phase III trial. Under the district court's unduly restrictive standard, Helsinn could not have filed a valid patent application before the critical date of January 30, 2002. Such a standard would preclude the filing of meritorious patent applications in a wide variety of circumstances. The evidence that the formulation was ready for patenting is overwhelming, and the District Court's contrary conclusion—applying the wrong standard—was clearly erroneous. There is simply no tenable argument that, before the critical date, Helsinn was unable to file a patent application that met the requirements of 35 U.S.C. § 112.[20]

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[20] *See Space Sys./Loral, Inc. v. Lockheed Martin Corp.*, 271 F.3d 1076, 1080 (Fed. Cir. 2001) ("To be 'ready for patenting' the inventor must be able to prepare a patent application, that is, to provide an enabling disclosure as required by 35 U.S.C. § 112. . . . [W]hen development and verification are needed in order to prepare a patent application that complies with § 112, the invention is not yet ready for patenting."); *Clock Spring, L.P. v. Wrapmaster, Inc.*, 560 F.3d 1317, 1328 (Fed. Cir. 2009) ("By filing the 1992 [patent] application, the inventors represented that the invention was then ready for patenting . . . ."); *see also In re Brana*, 51 F.3d 1560, 1568 (Fed. Cir. 1995) ("FDA approval, however, is not a prerequisite

The district court and Helsinn on appeal rely on our decision in *Omeprazole* to argue that the results from Phase III trials must be analyzed in order to draw a valid conclusion regarding whether the invention works for its intended purpose. *See Omeprazole*, 536 F.3d 1361. But there is no general rule that Phase III trials must be completed before a product is ready for patenting, just as there is no general rule that Phase III trials are irrelevant. Each case must be decided based on its own facts. And this case is not like *Omeprazole*. In *Omeprazole*, there was significant uncertainty going into Phase III trials regarding whether the formulation would "solve the twin problems of *in vivo* stability and long-term storage" that had been identified *after* Phase II trials. *Id.* at 1373 (internal quotation marks omitted). Indeed, between Phase II and Phase III the researchers needed to attempt "a number of modifications to the Phase II formulation" since achieving the "two goals seemingly conflicted." *Id.* Here, of course, there was no similar need to modify the formulation in between the Phase II and Phase III trials, as Helsinn stipulated to the formulation's stability.

We conclude that the invention was reduced to practice and therefore was ready for patenting before the critical date.

CONCLUSION

We hold that the asserted claims, claims 2 and 9 of the '724 patent, claim 2 of the '725 patent, claim 6 of the '424 patent, and claims 1, 2, and 6 of the '219 patent, are invalid under the on-sale bar.

REVERSED

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for finding a compound useful within the meaning of the patent laws.").

APPENDIX C

UNITED STATES DISTRICT COURT FOR THE DISTRICT OF NEW JERSEY

No. 11-3962 (MLC)

HELSINN HEALTHCARE S.A., et al.,
Plaintiffs,

v.

DR. REDDY'S LABORATORIES LTD.,et al.,
Defendants.

March 3, 2016

SUPPLEMENTAL OPINION

COOPER, District Judge.

This is an action arising under the Hatch-Waxman Act, 35 U.S.C. § 271(e)(2)(A). Plaintiffs, Helsinn Healthcare S.A. ("Helsinn") and Roche Palo Alto LLC ("Roche") (collectively, "plaintiffs"), are assignees of U.S. Patents No. 7,947,724 ("the '724 patent"), No. 7,947,725 ("the '725 patent"), No. 7,960,424 ("the '424 patent"), and No. 8,598,219 ("the '219 patent"). The four patents-in-suit are listed in the FDA "Orange Book" as covering plaintiffs' product Aloxi®, which is a pharmaceutical composition containing the active ingredient palonosetron. The version of Aloxi® currently marketed by plaintiffs is an

intravenous solution with approved indications for preventing or treating cancer chemotherapy-induced nausea and vomiting.

Plaintiffs brought this action, and related consolidated actions, against generic drug manufacturers, Dr. Reddy's Laboratories, Ltd., Dr. Reddy's Laboratories, Inc. ("DRL"), Sandoz, Inc. ("Sandoz"), Teva Pharmaceuticals USA, Inc., and Teva Pharmaceutical Industries, Ltd. ("Teva"). Plaintiffs alleged that each group of defendants had filed an Abbreviated New Drug Application ("ANDA") containing so called "Paragraph IV" certifications asserting that the claims of the patents-in-suit were invalid and/or not infringed. The asserted claims are claims 2 and 9 of the '724 patent, claim 2 of the '725 patent, claim 6 of the '424 patent, and claims 1, 2, 6, and 7 of the '219 patent. The pertinent limitations of the first three patents are "reducing emesis . . . ," the "0.05 mg/mL" concentration, and "EDTA." The pertinent limitations of the '219 patent are "reduce ... cancer chemotherapy-induced nausea and vomiting," "0.25 mg" dose in "5 mL . . . solution," and "EDTA."

Defendant Sandoz was dismissed from the action by consent, on December 31, 2014. (Dkt. 247.)[1] The Court is-

[1] The Court will cite to the documents filed in this case in the Electronic Case Filing System ("ECF") by referring to the docket entry numbers by the designation of "dkt." References to docketed materials are to ECF pagination. The two later-filed actions that have been consolidated into this lead case are Civil Action No. 11-5579 and Civil Action No. 13-5815. Copies of the four patents-in-suit are attached as exhibits to the pleadings, and are trial exhibits. We will simply cite to the patents by page or column and line number. Those patents are

sued a Memorandum Opinion construing certain preamble language in the '219 patent claims, on April 22, 2015. (Dkt. 290.) An 11-day bench trial was conducted in June 2015, with closing arguments presented on August 12, 2015. (Dkts. 320, 322, 324, 326, 328, 330, 331, 337, 340, 342, 344, and 353.) Defendant DRL was dismissed on stipulation on October 16, 2015. (Dkt. 355.)[2] Thus, the current parties in this case are plaintiffs and Teva.

Teva asserts that the asserted claims of each of the four patents-in-suit are invalid as obvious under 35 U.S.C. § 103.[3] Teva further asserts invalidity of those patents under the on-sale bar provision of 35 U.S.C. § 102. The on-sale bar issue presents not only underlying factual questions, but also a statutory interpretation question addressing the amended text of § 102(a)(1) under the America Invents Act ("AIA"), Pub. L. No. 112-29 (2011). Teva also raises a written description claim against those patents under 35 U.S.C. § 112. Plaintiffs oppose each of

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trial exhibits numbered as follows: '724 patent (DTX-0069), '725 patent (DTX-0070), '424 patent (DTX-0001 and DTX-0071), and '219 patent (DTX-0268).

[2] DRL and plaintiffs have a related action, actively pending in this Court, pertaining to the '724 patent and DRL's pending 505(b)(2) New Drug Application under 21 U.S.C. § 355(b)(2). See Helsinn Healthcare S.A., et al. v. Dr. Reddy's Laboratories, Ltd., et al., Civil Action No. 12–2867. In that case, the Court issued a Memorandum Opinion and Order on April 2, 2015, construing the '724 claim term "a chelating agent." (Civ. Action No. 12–2867, dkt. 91 (Order) and dkt. 92 (SEALED Mem. Op.).)

[3] Teva has advised that it will not appeal the ruling of this Court that the patents-in-suit are valid under 35 U.S.C. § 103 (obviousness). This Court will issue a separate Supplemental Opinion providing further rulings on that issue as necessary.

Teva's points on those issues, asserting that the patents are valid and enforceable.

There is also an infringement issue. Teva filed one consolidated ANDA, seeking approval for products at two different dose levels (0.25 mg and 0.075 mg), and two different treatment indications (chemotherapy-induced nausea and vomiting ("CINV") for the 0.25 mg dose, and post-operative nausea and vomiting ("PONV") for the 0.075 mg dose). The concentration of both proposed Teva products is 0.05 mg/ml, because the 0.25 mg dose solution is 5 ml and the 0.075 mg dose solution is 1.5 ml. The asserted '219 patent claims only specify a 0.25 mg dose, in a 5 ml volume (i.e., concentration 0.05 mg/ml), for CINV. Plaintiffs assert that if the '219 claims are held to be valid, those claims are infringed by Teva's ANDA filing itself, according to the Hatch-Waxman Act, and therefore both generic products applied for in Teva's ANDA must infringe and be enjoined. Teva disputes plaintiffs' legal position and seeks a declaration that its 0.075 mg dose PONV product will not infringe the asserted '219 patent claims.

The Court issued a Memorandum Opinion on November 13, 2015, and entered judgment declaring that:

(1) the asserted claims of the '724, '725, and '424 patents are valid and are infringed by both Teva's proposed 0.25 mg and 0.075 mg generic products;

(2) the asserted claims of the '219 patent are valid and are infringed by Teva's proposed 0.25 mg generic product; and

(3) the asserted claims of the '219 patent are valid and are not infringed by Teva's proposed 0.075 mg generic product.

(Dkt. 360; dkt. 361.)

This Supplemental Opinion constitutes the Court's findings of fact and conclusions of law on the issues of the on-sale bar under 35 U.S.C. § 102, statutory interpretation of the on-sale bar after the passage of the American Invents Act under 35 U.S.C. § 102(a)(1), written description under 35 U.S.C. § 112, and infringement under 35 U.S.C. § 271. The Court now makes the following findings of fact and conclusions of law pursuant to Federal Rule of Civil Procedure 52(a)(1).

1. FINDINGS OF FACT

A. Medical treatment for emesis

Medical science has long recognized that the human body has an elaborate and multifaceted defense system against trauma and toxins. (Dkt. 328 at 29.) Part of that defense system is called emesis, referring generally to the reflexive reaction experienced as nausea and vomiting. (Id. at 27, 31-32.) Its purpose is essentially to get rid of toxins in the body. (Id. at 26.)

The parties presented undisputed medical background information on the scientific field of the claimed inventions. (Id.; see also dkt. 320; dkt. 324; dkt. 326; dkt. 331; dkt. 337; dkt. 340; dkt. 342; dkt. 344.) For example, Teva's expert clinician Dr. David Frame provided a basic overview of the mechanisms in the body that lead to emesis, at least as related to chemical stimuli.[4] As he explained, the gastrointestinal tract and the brain are the

[4] Dr. Frame explained that he uses the term "emesis" to refer to vomiting, as distinguished from nausea. (See dkt. 328 at 31.) Other

two primary systems involved in creating emesis. (Dkt. 328 at 25–26.) If a person ingests a toxin directly into the stomach, or if a toxin is injected into the blood, the noxious substances go into the GI tract. (Id. at 26.) The GI tract then releases certain molecules called neurotransmitters. (Id.) Those neurotransmitters will bind to receptors, causing signals to transmit up a nerve called a vagal nerve that leads to a specific spot located in the brain but just outside the blood-brain barrier (the trigger zone or essentially the vomiting center). (Id.) When those neurotransmitter signals arrive there, they will activate one or more neurotransmitters that will carry the signal back down the vagal nerve to the GI tract and produce the contractions of nausea and vomiting. (Id. at 27.)

Scientists have identified approximately 20 to 30 types of neurotransmitters that play a role in prompting the emesis reaction. (Id. at 28.) Those neurotransmitters bind to cells called receptors, found in various places in the body. (Id. at 28–29.) In other words, several different neurotransmitters and corresponding receptors are involved in most causes of nausea and vomiting. (Id. at 29.) Also, depending on what kind of toxic stimulus is introduced, there may be different amounts and types of neurotransmitters activated, and different locations within the body where the corresponding receptors are concentrated. (Id. at 28–29.) All of this is part of that elaborate defense system against various toxic substances that is inherent in the body. (Id. at 26, 29.)

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witnesses and some of the prior art would use the term "emesis" more broadly to refer to nausea and vomiting. (See, e.g., dkt. 331 at 20.) We use the term in that broader sense, except when referring to testing results that pinpoint those aspects separately.

One of the neurotransmitters known to play a role in causing emesis is serotonin (5-hydroxytryptamine). (Id. at 28.) It can bind to many different types of receptors, but the one that it binds to that is most responsible for nausea and vomiting is a specific "hydroxytryptophan" receptor, called the 5-HT3 receptor. (Id. at 29.) Indeed, there are different types of hydroxytryptophan receptors, and the number 3 type (the "5-HT3 receptor") is known to be specific in binding with serotonin to release those nausea and vomiting signals. (Id.)

Some of the other types of neurotransmitters known to participate in prompting emesis (with corresponding varieties of receptors) are dopamine and something called Substance P that binds to neurokinin receptors. (Id. at 29, 33.) For this reason, among others, clinicians trying to prevent or treat emesis will often use a multifaceted approach. (Id. at 29.) Instead of relying on just one type of drug product, they will use a combination of therapies. (Id.) The pharmaceutical products used in this effort, that target various receptors and their corresponding neurotransmitters, are referred to as "antagonists." (Id. at 30.) Thus, compounds directed to serotonin and the 5-HT3 receptor are called "serotonin receptor antagonists" or "5-HT3 receptor antagonists." (Id.)

There are also timing and toxin factors in selecting "antiemetic" therapies. For example, some toxins used in medical treatment, or dosage levels of those toxins, are considered "highly emetogenic," whereas others may be considered "moderately emetogenic." (Id. at 148; dkt. 324 at 52.)

It is recognized that the onset and duration of emesis may vary, depending on the situation. (Dkt. 328 at 38.) So antiemetic therapy will look at effects in the immediate

time period after introduction of a toxin, as well as in the succeeding hours and days. (Id.) Those time periods are referred to as the "acute emesis" period for the first 24 hours, and "delayed emesis" thereafter. (Id. at 38–39.) These time periods are a recognized feature of designing and studying antiemetic care.

Another defining concept in the antiemetic field is the distinction between so-called "post-operative nausea and vomiting," or PONV, and "cancer chemotherapy-induced nausea and vomiting," or CINV. (Id.) Both sorts of reactions are encompassed within the general term "emesis," but clinicians typically will select antiemetic therapies with that distinction in mind. (Id.) For example, the claims of the '219 patent-in-suit are directed to "cancer chemotherapy-induced nausea and vomiting." See Section I.B. The claims of the other three patents-in-suit are directed more broadly to "emesis." (Id.)

Aloxi® is the brand name of plaintiffs' antiemetic product, listed in the FDA Orange Book as covered by the four patents-in-suit. The active ingredient in Aloxi® is palonosetron hydrochloride, which is a serotonin antagonist or so-called 5-HT3 antagonist. It is currently marketed in the United States in the form of an intravenous 0.25 mg dose in 5 ml solution (resulting in palonosetron concentration of 0.05 mg/ml). At that dosage, it has FDA-approved indications for preventing CINV in both moderately and highly emetogenic cancer chemotherapy, including delayed CINV with respect to the moderately emetogenic chemotherapy. (DTX-1244-0002.) A later-approved additional indication is at a one-third lower dosage of 0.075 mg for prevention of PONV, but it is not currently marketed in that form. (Id.; dkt 331 at 85.)

The compound Aloxi®, with its label information, received FDA approval on July 25, 2003, after a lengthy new drug application process. See n. 39 infra. The provisional patent application to which the four patents-in-suit claim priority was filed on January 30, 2003. The parties agree that the relevant date for analyzing prior art (as well as for the on-sale bar factual issues) is January 30, 2002. See n. 61 infra. As the discussion in this opinion will demonstrate, the patent validity issues in this case focus heavily upon the history of the Aloxi® drug development process in that time frame.

B. The patents-in-suit

The four patents-in-suit are each named "Liquid Pharmaceutical Formulations of Palonosetron." They are all composition patents. (Dkt. 290 at 2.) There are other patents and patent applications in the same patent family history. (Id.; dkt. 289.)

Each of the patents-in-suit claims priority to the original provisional application date, January 30, 2003, although they have different effective filing dates. (Dkt. 289.) In chronological order of issuance, they are the '724 and '725 patents, issued on May 24, 2011; the '424 patent, issued on June 14, 2011; and the '219 patent, issued on December 3, 2013. (Id.)

All four patents are subject to terminal disclaimer, and will expire no earlier than July 30, 2024. (Dkt. 361 at 3.) The parties agree that the first three patents are subject to the patent provisions in effect prior to enactment of the AIA, and the '219 patent is subject to the AIA for purposes of this case. In fact, the '219 patent was applied for and granted during the pendency of this litigation. (Dkt. 289.) This case was filed on July 8, 2011. (Dkt. 1.) The

effective application date of the '219 patent was May 23, 2013, after the pertinent effective date of the AIA. (Dkt. 289.)

The asserted claims are the '724 patent, claims 2 and 9; the '725 patent, claim 2; the '424 patent, claim 6; and the '219 patent, claims 1, 2, 6, and 7. (Dkt. 174 at 2.) This Court has issued a claim construction opinion that construed the preamble language of the asserted claims to be claim limitations. (Dkt. 290.)

Claim 2 of the '724 patent is representative of the asserted claims of the '724, '725, and '424 patents. Rewritten to incorporate claim 1 of the '724 patent on which it depends, claim 2 states:

> A pharmaceutically stable intravenous solution for reducing emesis or reducing the likelihood of emesis comprising:
>
> a) about 0.05 mg/ml palonosetron or a pharmaceutically acceptable salt thereof, buffered at a pH of from 4.0 to 6.0; and
>
> b) a pharmaceutically acceptable sterile aqueous carrier including a tonicifying effective amount of mannitol and from 0.005 mg/ml to 1.0 mg/ml EDTA.

('724 patent, col. 9, line 27, to col. 10, line 3.)

Asserted claim 1 of the '219 patent, on which asserted claims 2, 6, and 7 of that patent depend, states:

> A pharmaceutical single-use, unit-dose formulation for intravenous administration to a human to reduce the likelihood of cancer chemotherapy-induced nausea

> and vomiting, comprising a 5 mL sterile aqueous isotonic solution, said solution comprising:
>
> palonosetron hydrochloride in an amount of 0.25 mg based on the weight of its free base;
>
> from 0.005 mg/mL to 1.0 mg/mL EDTA; and
>
> from 10 mg/mL to 80 mg/mL mannitol,
>
> wherein said formulation is stable at 24 months when stored at room temperature.

('219 patent, col. 10, lines 1–12.)

The written descriptions of the four patents are generally similar. For example, the specification of each patent contains the following sentence, giving the exact dosage and/or concentration appearing in the asserted claims:

> In one particular embodiment the palonosetron is supplied in vials that comprise 5 ml. of solution, which equates to about 0.25 mg of palonosetron at a concentration of about 0.05 mg/ml.

(See '724 patent, col. 4, line 66, to col. 5, line 2; '725 patent (same); '219 patent (same); '424 patent, col. 5, lines 14–17.)

C. Factual chronology

It is necessary to set forth in detail the factual history of the pharmaceutical development process that led to the patents-in-suit, and to the marketing of Aloxi® as their commercial embodiment. That factual history is undisputed, but the parties differ sharply as to the legal conse-

quences of the facts, particularly in analyzing Teva's validity challenges based on both obviousness and the on-sale bar.

An important distinction must be borne in mind when reviewing this factual history. For purposes of the obviousness analysis, the focus must be on the state of the art as publicly known; that is, the published prior art and what a skilled artisan would have known. In fact, the actual process of invention that led to the claimed invention is considered irrelevant under obviousness analysis. See Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc., 520 F.3d 1358, 1364 (Fed. Cir. 2008). In sharp contrast, the legal tests for the on-sale bar require a court to look also at facts that were not public; for example, to determine whether the invention was "ready for patenting" more than one year before the patent application date. See Section II.A.4.

One fact that is pivotal to both the obviousness and the on-sale bar issues is that the provisional application date for all four patents-in-suit was January 30, 2003. (See dkt. 289.) Therefore, the date of January 30, 2002, is the critical date for purposes of the on-sale bar. See 35 U.S.C. § 102, amended by Leahy-Smith America Invents Act, Pub.L. No. 112-29, 125 Stat. 254 (2011). That same date of January 30, 2002, is also the date for obviousness analysis of the published prior art references, as stipulated by the parties. (Dkt. 328 at 240–41.)

Here we set forth both the publicly known and the behind-the-scene facts in recounting this history. In Section II the parties' arguments on their many legal issues are addressed by reference to these facts.

1. Syntex and the genus '333 patent

There was a group of scientists in Palo Alto, California, doing research in a company named Syntex (U.S.A.), Inc. ("Syntex"), beginning in the late 1980's. In May 1991, Syntex filed a patent application that resulted in issuance of U.S. Patent No. 5,202,333 ("the '333 patent") on April 13, 1993. (DTX-0343.)

The '333 patent disclosed "novel compounds which are 5-HT3 receptor antagonists," in particular, "tricyclic 5HT3 receptor antagonists containing a bridged bicyclic amine substituent." (Id., col. 1, lines 9–14.) There were three independent claims and many dependent claims. Claim 1 was to "a compound of Formula I," which was an extremely broad genus-type formula. (Id., col. 34, line 15, to col. 35, line 14.) Independent claim 40 made the following pharmaceutical composition claim:

> A pharmaceutical composition for treating a condition chosen from emesis, a gastrointestinal disorder treatable with prokinetic agents, anxiety/depressive state, and pain, which composition comprises a therapeutically effective amount of a compound of claim 1 in combination with a pharmaceutically acceptable carrier.

(Id., col. 37, lines 10–17.) Independent claim 41 claimed a method for treating a condition chosen from those disorders, "in an animal in need of such treatment." (Id., col. 37, lines 18–24.)

"Emesis" was a defined term in the '333 patent, quoted here in the margin.[5] "Disease" was defined to include "the emesis caused by therapy with agents having emetogenic side effects, in particular by therapy for cancer, such as chemotherapy with cytotoxic agents ...." (Id., col. 4, lines 33–41.) "Treating" was defined to include preventing, inhibiting, or relieving the "disease." (Id., col. 5, lines 33–40.)

The Background of the Invention section of the '333 specification explained serotonin and its receptors, in pertinent part as follows:

> Serotonin, a neurotransmitter with mixed and complex pharmacological characteristics, was first discovered in 1948 and subsequently has been the subject of substantial research. Serotonin, also referred to as ... (5-HT), acts ... on discrete 5-HT receptors ... [which] are presently delineated into three major subclassifications -- 5-HT1, 5-HT2 and 5-HT3 .... Receptors of the 5-HT3 subclass ... appear to regulate the release of a variety of neurotransmitters in the gastrointestinal, cardiovascular and central nervous systems.
>
> 5-HT3 receptors are located in high densities on neurons associated with the emetic reflex and drugs which block the interactions of serotonin at the 5-HT3 receptor level, i.e., 5-HT3 receptor antagonists, possess po-

[5] The '333 written description stated: "'Emesis', for the purposes of this application, will have a meaning that is broader than the normal, dictionary definition and includes not only vomiting, but also nausea and retching." (DTX-0343, col. 4, lines 42–45.)

> tent antiemetic properties. Such antagonists demonstrate utility for counteracting the emetic effects of cancer chemotherapy and radiotherapy.

(Id., col. 1, lines 19–41.)

The parties agree that palonosetron is one of the myriad compounds claimed within Formula I of the '333 patent, although the exact chemical name and structure of palonosetron is not specified.[6] The number of compounds claimed in the '333 patent is not quantified in the patent itself or in any of the trial evidence, but expert testimony at trial indicated that the amount of possible combinations that could be claimed within the patent formula was "huge." (Dkt. 328 at 172.)

The '333 specification reported that the inventors had employed accepted testing methods to determine activity of "the compounds of Formula I" in animals. (DTX-0343, col. 11.) That testing included in vitro assay of rat brain tissue, as well as in vivo testing of anesthetized rats, to measure 5-HT3 "receptor binding affinity" of the compounds. (Id., col. 11, lines 5–11.) It also included in vivo measurement of "anti-emetic activity" of the compounds in reducing emesis induced by a chemotherapy agent (specifically, cisplatin) in ferrets and in dogs. (Id., col. 11, lines 11–35.)

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[6] Teva's formulator expert, Dr. Kirsch, identified this language in the '333 specification as including palonosetron: "Of most interest are the compounds of Formula I in which each p, q and u are O, and R3 is 1-azabicyclo[2.2.-2]oct-3-yl, in particular wherein one or, when present, both chiral centers possess S configurations." (Dkt. 326 at 189 (quoting DTX-0343, col. 9, lines 23–26).)

As seen in the claim language of the '333 patent, the planned uses of its compounds were not confined to antiemetic treatment. (Id., col. 37, lines 10–26; col. 38, lines 1–7.) Other "diseases" such as gastrointestinal disorders, anxiety, and pain were also listed. (Id., col. 37, lines 18–23.) When discussing administration of the claimed compounds, the '333 specification gave correspondingly broad descriptions of possible routes of administration,[7] dosing levels,[8] and drug concentration formulations,[9] as quoted in

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[7] The '333 specification stated: "In general, compounds of Formula I will be administered as pharmaceutical compositions by one of the following routes: oral, systemic (e.g., transdermal, intranasal or by suppository) or parenteral (e.g., intramuscular, intravenous or subcutaneous)." (DTX-0343, col. 12, lines 25–29.)

[8] The '333 specification addressed dosage of a "pharmaceutically effective amount" as follows:

> A therapeutically effective amount may vary widely depending on the severity of the disease, the age and relative health of the subject, the potency of the compound used and other factors. Therapeutically effective amounts of compounds of Formula I may range from approximately 1.0 nanogram per Kg (ng/Kg) body weight per day to 1.0 mg/Kg body weight per day. Preferably the amount will be approximately 10 ng/Kg/day to 0.1 mg/Kg/day. Therefore, a therapeutically effective amount for a 70 Kg human may range from 70 ng/day to 70 mg/day, preferably 700 ng/day to 7.0 mg/day.

(DTX-0343, col. 12, lines 7–18.)

[9] The '333 specification discussed drug concentration as follows:

> The amount of a compound of Formula I in the composition may vary widely depending upon the type of formulation, size of a unit dosage, kind of excipients and other factors known to those of skill in the art of pharmaceutical sciences. In general, the final composition will comprise from 0.000001% w to 10.0% w of the compound of Formula I, preferably 0.00001% w to 1.0% w, with the remainder being the excipient or excipients. (DTX-0343, col. 12, lines 60–68.)

the margin. Regarding dosage, the specification also stated: "One of ordinary skill in the art of treating such diseases will be able, without undue experimentation and in reliance upon personal knowledge and the disclosure of this application, to ascertain a therapeutically effective amount of a compound of Formula I for a given disease." (Id., col. 12, lines 19–24.)

The '333 patent specification provided Example 13 as "representative pharmaceutical formulations containing a compound of Formula I." (Id., col. 28, lines 55–56.) It included examples for an oral solution, an intravenous solution, and a tablet.

The intravenous formulation in Example 13 was:

Compound of Formula I	10-100mg
DextroseMonohydrate	q.s. to make isotonic
Citric Acid Monhydrate	1.05 mg
Sodium Hydroxide	0.18mg
Water for Injection	to 1.0ml

(Id., col. 29, lines 6–11.)

The Syntex inventors continued their research involving the compounds claimed in the '333 patent into the mid-1990's, as described next.

2. Roche Syntex further development process

Syntex pursued the development of its '333 patent compounds through several steps in its research process. That research included the laboratory studies referred to in the specification of the '333 patent, and other studies documented in its own internal "formulation books." (Dkt. 320 at 27–28.)

Syntex filed an Investigational New Drug ("IND") application, number 39,797, with the FDA on June 2, 1992. (See PTX-261.0002.) The subject of the IND was investigation of palonosetron hydrochloride, designated RS-25259-197 ("RS-25259"). (See id.)

As Helsinn later stated to the FDA, in summarizing the Syntex preclinical (animal) studies leading to that IND application, "[e]xtensive *in vitro* and *in vivo* pharmacologic studies for palonosetron have been conducted." (DTX-293-0031.) Among the key findings from those studies was that palonosetron "has a high affinity and specificity for 5-HT3 receptors," and "[p]alonosetron is effective in animal modes of chemically induced emesis by both oral and intravenous routes." (Id. at -0031 to -0032.)

The Syntex research under its IND progressed through Phase I and Phase II clinical testing of RS-25259. (See dkt. 320 at 30–32.) The Phase I clinical studies were to determine safety and pharmacokinetics of the palonosetron, by administering it as an intravenous injection to healthy human volunteers. (DTX-0293-0032.) Once the Phase I clinical studies were complete and indicated safety of the drug, Syntex obtained FDA approval and proceeded to Phase II studies, which it worked on through approximately 1995. (Id. at -0032 to -0035; dkt. 320 at 31–32.) The pharmacokinetic data from the Phase I studies also indicated that "[t]he mean plasma elimination half-life . . . was approximately 40 hours in subjects given single IV or oral doses." (DTX-0293-0033.)

Generally, in a Phase II clinical study, the active pharmaceutical ingredient ("API") is administered to actual patients, to continue assessing safety but also to start determining effective dosage levels in humans. (See dkt. 320 at 31.) If Phase II studies are completed and accepted by

the FDA, the applicant may request to proceed to Phase III, which is typically a large-scale study conducted with an actual pharmaceutical formulation, including excipients and packaging, involving patients in many locations. In Phase III, the safety and efficacy of the formulation is measured in the patients, and stability and manufacturing quality of the product are tested in samples. (Id.)

Syntex was acquired by the Roche pharmaceutical organization ("Roche") at some time prior to 1995. (Dkt. 320 at 127.) Syntex was then known as Roche Syntex, or officially Roche Palo Alto LLC. (See id.; '724, '725, '424, and '219 patents, page 1.)

Several Phase II clinical trials to evaluate safety and efficacy of palonosetron hydrochloride were conducted by Roche Syntex under its IND. Again as later summarized to the FDA by Helsinn, those studies were as follows:

> Study 2330: Intravenous for prevention of highly emetogenic CINV.[10]
>
> Study 2332: Oral for prevention of highly emetogenic CINV.
>
> Study 2500: Intravenous for PONV.
>
> Study 2502: Oral for PONV.

(See DTX-0293-0033.)

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[10] There was another Phase II clinical trial also directed to intravenous use in prevention of highly emetogenic CINV (Study 2120), but it was discontinued due to poor patient enrollment. (See PTX-261.0002.)

The Phase II Study 2330 ("the 2330 study") was named "A dose-ranging, efficacy, safety, and pharmacokinetic study of single intravenous doses of RS-25259 for prevention of nausea and vomiting in chemotherapy-naive cancer patients receiving highly emetogenic chemotherapy." (DTX-0227-0005.) That study started in May 1994. (See id.) The Final Report of that study was dated July 1995, and signed on September 25, 1995. (DTX-0227-0005, -0016.)

The Introduction section of the 2330 study Final Report stated in part as follows:

> Cancer chemotherapy may be associated with a high incidence of nausea and vomiting, particularly when certain agents such as cisplatin are used. Nausea and vomiting may be triggered by the release of . . . (5-HT) via a cascade of neuronal activation involving both the gastrointestinal tract and the central nervous system. Emesis may be seen acutely (within 24 hours of the start of chemotherapy), after a delay (beginning 24–48 hours after chemotherapy), or even in anticipation of chemotherapy . . . . With repeat courses of chemotherapy, emesis becomes progressively more difficult to control, although adequate control in the first chemotherapy cycle is more likely to be associated with control of acute emesis in subsequent cycles. Therefore, antiemetic efficacy is generally studied first in chemotherapy-naive patients.
>
> In the United States, currently available antiemetic therapies include either single-drug or combination therapy with phenothiazines, steroids, or metoclopramide (a mixed 5-HT3 and dopaminergic-receptor antagonist), or most recently ondansetron (a 5-HT3 receptor antagonist). All of these therapies must be

> given as multiple-dose regimens because of their short half-lives, and none is completely effective in preventing the severe nausea and vomiting associated with cancer chemotherapy.
>
> RS-25259-197 (hereafter referred to as RS-25259) is a novel, potent, and selective 5-HT3 receptor antagonist. In animal models of chemotherapy-induced emesis, RS-25259 completely inhibits emesis in up to 100% of animals given high-dose cisplatin. In humans, the mean half-life of the drug is approximately 40 hours, whether administered intravenously or orally. Given the high affinity for the receptor, excellent efficacy in animals, and long half-life in humans, a single dose of RS-25259 may control acute chemotherapy-induced emesis.
>
> This was the first randomized, double-blind trial of intravenously administered RS-25259 in chemotherapy-naive cancer patients.

(DTX-0227-0017 to -0018 (footnotes omitted).)

The stated objectives of the 2330 study included: "(1) [to] determine the dose-response relationship among single IV doses of RS-25259 over the dose range 1-90 μpg/kg . . . . " (Id. at -0014.) The Final Report of the 2330 study concluded as follows:

> RS-25259, administered as a single intravenous bolus injection of 3, 10, 30, or 90 μpg/kg 30 minutes prior to high-dose cisplatin chemotherapy, was effective in suppressing chemotherapy-induced emesis for 24 hours. All four doses were approximately equally effective as compared with the combined results from a cohort of 0.3 and 1 μpg/kg.

. . . .

> Based on the results of this study, a dose of 3 μg/kg or 10 μg/kg RS-25259 might be appropriate for further development.

(Id. at -0015 to -0016.)

The 2330 study Final Report also noted the following pharmacokinetic observations: "The plasma half-life was exceptionally long for this class of compound, and a few patients demonstrated very long half-lives compared with the other patients." (DTX-0227-0016.)

There were, however, significant questions about effective dosage levels remaining at the end of the 2330 study, as described in that same 2330 study Final Report. The Discussion section of the Report stated as follows:

> A statistically supported dose-response relationship for efficacy . . . between the lowest dose level of RS-25259 and each subsequent higher dose level was not observed in this study. The statistical analyses, defined prior to study start, were essentially confounded by the relatively high response rate observed among patients who received the lowest dose of RS-25259, namely 0.3–1 μg/kg. This was not expected and the reasons for this response are unclear. One could perhaps speculate and perform additional statistical tests, but that would be beyond the scope of the preplanned analysis.
>
> Nevertheless, based on published data that shows that almost all patients who receive high doses of cisplatin experience nausea and vomiting, the results of this study suggest that RS-25259 is an effective agent.

> Based on clinical observation, a single intravenous bolus injection of 3, 10, 30 and 90 μg/kg RS-25259 30 minutes prior to cisplatin chemotherapy was effective in suppressing chemotherapy-induced emesis for 12 to 24 hours . . . . Although no placebo control was incorporated into the design of this study, there appeared to be a step up in efficacy from the combined 0.3–1 μg/kg dose group to doses of 3 μg/kg and more. The four highest doses were approximately equally effective when compared with the results from the combined 0.3–1 μg/kg cohort, suggesting a plateau in the dose response for RS-25259 when administered at a dose greater than 3 μ g/kg. RS-25259 was well tolerated in this study. No safety issues related to RS-25259 were apparent.

(Id. at -0055.)

When Helsinn later approached the FDA for permission to commence Phase III clinical trials, these facts and the underlying data reflected in the 2330 study led the FDA to conclude that the 2330 study itself did not provide any reliable dose response data, except possibly at the much higher 30 microgram per kilogram level. See Section I.C.5.

The dosages measured in the Phase II 2330 study were expressed in micrograms of palonosetron per kilogram of patient body weight, i.e., "weight-based" measurements, as stated in the above-quoted passage. At trial there was no dispute that the "3 microgram per kilogram" figure, expressed in that Report, is approximately the numerical equivalent of the 0.25 milligram dose actually claimed in the '219 patent for treatment of CINV. (See, e.g., dkt. 322 at 121.) In the Phase III trials for CINV treatment, described below, Helsinn chose to study

"fixed-dose" amounts of 0.25 mg dose and 0.75 mg dose. (See id. at 132.) The 0.75 milligram dose likewise corresponds to the "10 microgram per kilogram" figure in the 2330 study. (See PTX-182.0009 to .0010.)[11]

The 2330 study was a well-designed study in that it was randomized, double-blind, and multi-center. (See DTX-0227-0014.) On the other hand, as was appropriate for such a Phase II study, it involved only a small number of patients (161 patients, of which 18 were excluded from the efficacy results for valid reasons), and the total number of patients receiving each dose level ranged between only 24 and 46. (Id.)

There was also no formulation data at all in the 2330 study, on stability or any other properties, because the palonosetron was simply diluted in saline solution and buffered for injection. (Id. at -0015; dkt. 324 at 86- 89.) In that form, it was not stable at room temperature and required refrigeration and resupply in the course of the study. (Dkt. 322 at 102.) In fact, although the Roche Syn-

[11] The following table of conversion equivalents from weight-based dose units to fixed-dose units is contained in the Helsinn Phase III data, and was not disputed at trial:

Weight-based dose groups	Fixed dose groups
0.3 μg/kg – 1 μg/kg	<0.1 mg
3 μg/kg	0.25 mg
10 μg/kg	0.75 mg
30 μg/kg	2 mg
90 μg/kg	6 mg

(PTX-182.0010.)

tex formulation books contained some research on possible formulations, that work had not progressed to the actual making of any formulations, complete with excipients, that could have been used for Phase III clinical studies. (Id. at 103–04.)

By 1997, as described below, Roche had discontinued work on the Roche Syntex palonosetron project, deciding not to proceed with it after completion of the Phase II studies. (Id.)[12] At that time, Roche made Helsinn aware that Roche was interested in selling a license on the rights to palonosetron and the existing development research. (Id. at 80.) After a due diligence period under confidentiality restrictions, Helsinn did enter into that license agreement with Roche in early 1998, and began its work on further development of palonosetron into a pharmaceutical product. (Id. at 31, 49.)

3. Helsinn license from Roche

Plaintiff Helsinn Healthcare S.A. ("Helsinn" or "HHC") is a family-owned and family-run Swiss company with headquarters in Lugano, Switzerland. (Dkt. 320 at 108; dkt. 322 at 76–77.) The Roche pharmaceutical organization is a large corporate entity that also has a headquarters in Switzerland. (Dkt. 322 at 86.) In the 1997–1998

[12] The Syntex scientists who had developed the palonosetron hydrochloride compound and taken it through the Phase II stage of development did publish a few materials in the 1995–1998 time period. Those publications were later listed as prior art references in the patents-in-suit. (See, e.g., '724 patent, page 1, listing references by R.M. Eglen, J. Chelly, and J. Tang.) Those references, and a 2001 set of abstracts by Helsinn researcher G. Piraccini (also identified as prior art in those patents), are particularly relevant to the obviousness issues in this case, as discussed in the testimony of the parties' expert witnesses on those issues.

time frame, Roche and Helsinn would periodically communicate about potential licensing arrangements. (Id.) That is how Helsinn was informed that Roche had decided to terminate its palonosetron development project at the conclusion of the Phase II studies and was interested in licensing out the rights to the project. (Id. at 86–87.).

The Helsinn organization at that time had been managed by the founder, Gabriele Braglia, who was transitioning the leadership of the company to his sons, Enrico and Riccardo Braglia. (Id. at 86.) Dr. Giorgio Calderari is a Ph.D. chemist and current group general manager and chief operating officer at Helsinn in Lugano. (Dkt. 320 at 106.) He is a named inventor in the four patents-in-suit. (Id.) He testified at length at trial, called as a witness by both sides. (Dkt. 320 at 105–225; dkt. 322 at 9–175.)

Dr. Calderari recalled that when he joined the organization in 1985, it was a small company with a staff of about 20 employees at Lugano and another 15 employees at its chemical plant in Biasca, Switzerland. (Dkt. 322 at 77–78.) In the 1997–1998 time period, before Helsinn began its development of palonosetron, its organization had grown to approximately 200–250 employees. (Id. at 78.) Its operations were located as before in Lugano and Biasca, as well as in a finished drug product plant in Ireland at a subsidiary, Helsinn Birex Pharmaceuticals Ltd. ("Helsinn Birex"). (Id. at 77; dkt. 320 at 202.) At that time, its major product was an anti-inflammatory drug that was sold in Europe and South America, but sales were declining because it was going off patent, and Helsinn had no products in the United States pharmaceutical market. (Dkt. 322 at 77, 87.)

The business plan of Helsinn, at the time it licensed palonosetron from Roche in 1998, was described by Dr.

Calderari as a "business-to-business" model. (Dkt. 320 at 110–11.) Helsinn would take licenses from others who had developed new chemical entities and continue that development process, while simultaneously seeking partners for eventual worldwide distribution. (Id.) In other words, it was looking to in-license drug development projects and try to take them through to the marketing and distribution stage with others. (Id.) Helsinn was not a drug discovery company at that time, and it did not have its own sales force. (Id. at 111.) Nor did it have its own formulation research and development laboratories. (Dkt. 330 at 7–8.) It would obtain those services from contract research organizations ("CROs") and contract manufacturing organizations ("CMOs"). (Id. at 7.)

When Helsinn was considering the prospect of acquiring the palonosetron development rights from Roche, it had full access to Roche Syntex's laboratory and Phase II documentation, and it was able to speak with the scientists there. (Dkt. 320 at 114–15; dkt. 322 at 81.) Dr. Calderari was part of the team at Helsinn that was responsible for evaluating that opportunity. (Dkt. 320 at 114.) He testified that the Helsinn team's view of the project, after making its due diligence review, was that from a scientific standpoint it could enable Helsinn to enter a new field of research, and it could be an opportunity for Helsinn to enter the U.S. market, "but we were also aware that there was some risk that we would have to overcome in order to arrive at a successful product." (Dkt. 322 at 87.)

The class of molecules known as 5-HT3 receptor antagonists, commonly called setrons, had already been developed into pharmaceutical products, although none of the setron molecules covered by Roche Syntex's '333 patent had yet been developed to that point. (Id. at 80.) At

that time in early 1998, there were already three setron products on the market in the U.S., namely ondansetron, dolasetron, and granisetron. (See id. at 89.) They were sold by major companies including GlaxoSmithKline and Sanofi-Aventis.[13] (Id. at 92.) Those products contained different setron compounds, but Helsinn understood that they were considered interchangeable. (Id. at 91.)

The palonosetron project documents reviewed by Helsinn showed that Roche itself, in view of Syntex's Phase II testing, did not see any particular efficacy advantages of palonosetron compared to the existing setron products, nor did it see market potential. (Id. at 81–82.) So even if Helsinn were to succeed in developing a commercial formulation and obtaining FDA approval after Phase III clinical trials, the palonosetron product would be a fourth setron in the same class, a so-called "me too" compound. (Id. at 82.) It would likely earn only modest sales, according to Roche's projections. (Id. at 83.) Furthermore, the earliest of those setrons, ondansetron, was losing its patent protection in 2005. (Id. at 144.) Roche charged Helsinn a relatively modest sum, $10 million, for the license rights to palonosetron, with further royalties due only if and when a product was approved and launched. (Id. at 84.)

Helsinn was also aware, from scientific publications, that at that time many companies including Roche were developing or were looking to another class of antiemetic products called NK-1, referring to neurokinin receptor

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[13] Zofran®, or ondansetron, was approved by the FDA for the treatment of CINV in January 1991. (Dkt. 330 at 155.) Kytril®, or granisetron, was approved by the FDA for treatment of CINV in December 1993. (Id. at 156.) Anzemet®, or dolasetron, was approved by the FDA for the treatment of CINV in September 1997. (Id.)

antagonists. (See id. at 85.) In fact, at a later time, in or about 2005, Roche licensed to Helsinn an NK-1 compound named netupitant, and Helsinn took it from the end of Phase I trials through FDA approval and its launch in the U.S. in 2014. (Id. at 86). Also Roche, even while discontinuing its palonosetron project and licensing it to Helsinn, and while pursuing development of new NK-1 compounds, actually purchased the rights to the patented 5-HT3 product granisetron some years after 1998, paying over $1 billion for that deal as reported in the press. (Id. at 84.)

Aside from predicted poor marketing prospects for the palonosetron project, there were also technical problems confronting Helsinn as it considered whether to in-license the project. (Dkt. 320 at 124–25.) Helsinn studied Roche Syntex's efficacy records at the end of Phase II, including the results of the Phase II study 2330, which was for treatment of CINV. (Dkt. 320 at 31–32.) In their internal records at the end of Phase II, the Syntex scientists themselves had recommended that for a CINV indication (as contrasted with a PONV indication, which would typically be at a lower dosage), the minimum dose to be selected for Phase III trials should be 1.0 milligram, not the equivalent of 0.25 or 0.75 milligram doses suggested in the 2330 study conclusions. (Dkt. 322 at 111–12.)[14]

The Syntex scientists had also recommended (but not prepared or tested) a formula concentration level of 0.4 milligrams of palonosetron per milliliter of solution for the CINV Phase III trials. (Dkt. 322 at 111.) However, the

[14] Helsinn's PONV clinical expert, Dr. Keith Candiotti, testified that CINV dosage of setrons was generally higher than PONV dosage. (Dkt. 331 at 85.) Teva's clinical expert, Dr. David Frame, testified to the same effect. (Dkt. 328 at 121–22.)

Syntex formulation studies indicated that "[t]he higher the drug concentration in the solution, the less stable it becomes." (Id. at 113.) So stability itself was an issue, but so were dosage and concentration. (Id.) As Dr. Calderari summarized the situation:

> The problem is that from a chemical point of view, you wish to have the lowest possible concentration . . . because this increased the probability of having a stable solution. On the other hand, for showing efficacy, you have to have a dose or a concentration which is enough high [sic] so that the product will be at the end efficacious in the patient.

(Id. at 114–15.)

Keeping in mind all of those considerations, Helsinn did make the decision to proceed with the palonosetron project, entering into the license with Roche in early 1998. (See id. at 49.) As part of that deal, ownership of all the remaining developmental batches of the palonosetron API was transferred to Helsinn. (Id. at 104.) Roche specified that those supplies of API could be used only for developmental purposes, including Phase III clinical trials; that API could not be used for a commercial product. Helsinn complied with that restriction. (Id. at 104–05.)

Helsinn began its work under the license agreement with Roche by building a "project team." (Dkt. 320 at 109.) Dr. Calderari was in charge of the "chemistry manufacturing and control" ("CMC") part. (Id. at 109–10.) He explained that involved "developing the API . . . drug processes [and] quality control, up to having everything ready for the release and collecting all the necessary chemical stability data for filing a New Drug Application." (Id. at 110.) Dr. Calderari was assisted in those functions

by Dr. Daniele Bonadeo, whose degree was in chemistry and pharmacy and who also became a named inventor on the patents-in-suit. (Dkt. 330 at 5-6.)[15]

The dose selection and clinical studies for Helsinn's project were supervised by Dr. Alberto Macciocchi, a medical doctor who was also a Helsinn employee, in consultation with Dr. Calderari and his CMC group. (Dkt. 322 at 48, 119.)[16] There were also chemical people at Helsinn's own API manufacturing plant, and regulatory staff, as part of the Helsinn project team. (Dkt. 330 at 9.) In addition, Helsinn engaged a former Syntex scientist, Thomas Malefyt (another named inventor on the four patents-in-suit), who had been the CMC leader of the Roche Syntex palonosetron project team. (Dkt. 322 at 99–100.) He rendered a consulting report addressing the related issues of stability, dose selection, and concentration in designing the Phase III trials. (Id. at 115–16.) As Dr. Bonadeo testified, "the aim . . . was to have an NDA for CINV use of palonosetron." (Dkt. 330 at 9.)

There were substantial communications between the Helsinn project team and the former Syntex researchers, as well as other specialist consultants engaged by Helsinn, during the period starting in 1998 when Helsinn licensed the palonosetron project from Roche Syntex.

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[15] Dr. Bonadeo was deposed in this action, and portions of his testimony were placed in evidence at trial. (Dkt. 330 at 5–37.)

[16] Dr. Macciocchi passed away in approximately the mid-2000's. (Dkt. 322 at 48.) However, he was still functioning as project supervisor in the clinical area when Helsinn received the first of the Phase III preliminary results and forwarded them to the FDA in early 2002. (Id. at 59–65.) He continued in that same position to the end of Phase III and beyond, and he signed all of the Phase III final Clinical Study Reports. (DTX-0288-0004; DTX-0289-0003; DTX-0290-0003.)

Much of that work involved studying the Syntex Phase II clinical data and considering what doses and concentrations of palonosetron to recommend to the FDA for Phase III clinical trials.

Helsinn confidential records in that period include minutes of a week-long meeting in Palo Alto, California from July 20 to July 24, 1998 ("1998 Helsinn Clinical Meeting Minutes"). The persons attending that meeting included Dr. Macciocchi and Dr. Calderari from Helsinn; former Syntex researchers including Mr. Malefyt; Dr. David Gandara from University of California Davis, a prominent medical oncologist (see dkt. 324 at 45–46); and other doctors and scientists.

The summary of that meeting, as reported in the Minutes, stated in part:

> **Overview**
>
> . . . . After much consideration, and pending further statistical analyses of the phase 2 data, the following drug doses and concentrations are proposed for the CINV . . . trials.
>
> | Dose | mg/ml |
> |---|---|
> | 0.25 mg | 0.05 |
> | 0.75 mg | 0.15 |
> | 2.0 mg | 0.4 |
>
> . . . .
>
> **Planned data analyses**
>
> A further analysis of the phase 2 data is important, including

- by sex,
- μg/kg converted to per mg dosing,
- splitting the 0.3 and 1 pg/kg doses, and
- conducting a pk/pd analysis.

2. Safety should be reviewed by mg dosing.

3. Phase 1 volunteer data (pk) should be compared with phase 2 patient pk data.

4. The long half-life should be investigated on a per patient basis.

5. Phase 2 days 2-5 should be analyzed further (and evaluate in comparison with ondansetron days 2-5).

(DTX-0015-0008 to –0009.)[17]

4. The Oread agreements

Helsinn was aware that it would need manufacturing and testing capabilities in order to proceed to Phase III trials. (Dkt. 322 at 123–24.) The immediate need was to be able to create sufficient quantities of an actual formulated composition for use in the Phase III clinical studies. (Id.) That formulation would contain the palonosetron API batch material Helsinn had purchased from Roche, if the

[17] In the detailed contents of the 1998 Helsinn Clinical Meeting Minutes, it was noted that "Gandara recommended that, despite the unusual result in 2332 [the Phase II study on oral palonosetron for highly emetogenic CINV], 3 μg/kg was most likely the correct dose for CINV." (DTX-0015-0012 (bracketed text added).)

FDA agreed. (Id. at 123.) It would also contain the excipients that Helsinn would select for inclusion in the intravenous formulation that would be administered to the Phase III subject patients.[18] That Phase III intravenous formulation would be subject to FDA supervision as to manufacturing quality. (Id. at 135.) It would also have to be tested for properties including quality and stability, with those results reported to the FDA before and during the Phase III process. (Id. at 134–35.)

Looking beyond the Phase III trial period, if Phase III was successful and Helsinn decided to try to market a product based on that IND in the U.S. market, Helsinn would have to file a New Drug Application. One of the many requirements of Helsinn's NDA filing would be to document how and where the applied-for product or products would be manufactured and packaged for commercial distribution. (Id. at 135–36.) In connection with any such NDA, sample batches of commercial product would have to be submitted to the FDA, with full manufacturing documentation. Helsinn would need to arrange for the manufacture of new palonosetron API supplies for commercialization because as noted above, Helsinn's license from Roche did not permit the Syntex-made API supplies to be used in any commercial products.

Even before the license between Roche and Helsinn was finalized in early 1998, Helsinn had entered into a Confidential Disclosure Agreement, dated November 25, 1997, with a company named Oread, Inc. ("Oread") for the purpose of exploring a development and manufacturing

[18] According to Dr. Calderari, before Helsinn licensed the palonosetron development project from Roche, Syntex had made the determination to pursue an intravenous formulation for purposes of the Phase III trials. (Dkt. 322 at 23–24.)

relationship ("Oread Confidentiality Agreement"). (See DTX-0391-0002.) Oread was a company located in California, on the same campus as Syntex. (Dkt. 320 at 159.) It was an entirely separate company, not related to Helsinn. (See id.) Some of the personnel at Oread had come from Syntex, including Kathleen M. Lee, who later was named as one of the inventors on the patents-in-suit. (See DTX-1023-0001; dkt. 322 at 170–71.)

On July 13, 1998, Helsinn and Oread signed a contract entitled "Development and Manufacturing Agreement" ("Oread Development Agreement"). (DTX-0391-0001, et seq.) That Development Agreement expressly incorporated the confidentiality restrictions contained the Oread Confidentiality Agreement. (Id. at -0002.)

There were a number of functions that Oread contracted to perform under that Development Agreement, as generally described in its Exhibit A, Part I, Statement of Work, and as explained in the testimony of Dr. Calderari. (Id. at -0009; dkt. 320 at 172–176; dkt. 322 at 122–30.) Those functions included analytical and formulation development work, as well as taking the Syntex-manufactured palonosetron API owned by Helsinn (located in Boulder, Colorado, see dkt. 320 at 195), and manufacturing "developmental batches" of product formulation. (Dkt. 320 at 176.) That formulation would be used both for Phase III stability and quality testing, and for administration to patients in the Phase III clinical trials. (Dkt. 322 at 134–35.) The Oread Development Agreement also specified that Oread would perform the stability testing on the developmental formulation batches. (DTX-0391-0009.)

The Oread Development Agreement stated that Helsinn would provide sufficient palonosetron API to Oread for the Phase III clinical formulation manufacturing; and

the Oread scope of work expressly did not include any API development and manufacture. (Id.) In other words, as Dr. Calderari explained, "we would give our API to them, and they would use them to prepare the . . . formulation batches, for then giving us back to prepare to investigate in the Phase III clinical trials." (Dkt. 322 at 123–24.) He also testified that although Helsinn and Oread had discussions about Oread's potential capacity "in helping us in the future manufacturing commercial batches," no such agreement was ever reached. (Id. at 125; see also dkt. 320 at 160–61.)

Helsinn and Oread commenced working together under the Oread Development Agreement dated July 13, 1998, and continued those activities until Oread suddenly went out of business in mid-2000, during the Phase III trials, leaving Helsinn to find a substitute contractor. (Dkt. 320 at 169–70.) The functions that Oread did perform under contract during that period, for which it was paid by Helsinn, are summarized below.

5. FDA meeting March 10, 1999

Armed with all the existing Roche Syntex project information and its evaluations of that information, Helsinn notified the FDA that the Roche Syntex IND 39,797 had been transferred to Helsinn. In a December 23, 1998 submission to the FDA, Helsinn "described plans to develop palonosetron hydrochloride injection for the prophylaxis of . . . (CINV), . . . summarized palonosetron's clinical development to date and requested an End of Phase II meeting." (PTX-261.0002.) The stated purpose of the meeting was "to get the Division's input on (1) the planned phase III development program, (2) . . . the adequacy of the technology transfer program of drug substance from

the Syntex Boulder facility to the Helsinn Switzerland facility, and (3) . . . the sufficiency of the preclinical data to support a future NDA." (Id.)

The "End of Phase II" meeting was conducted at the FDA on March 10, 1999, and official minutes of the meeting were prepared by the FDA and distributed to the participants. (Id. at .0001) The meeting was attended by numerous listed FDA representatives, representatives of Helsinn including Dr. Calderari and Dr. Macciocchi, and consultants for Helsinn who were also named in the minutes.[19] In preparation for that meeting, Helsinn had provided the FDA with a "briefing package," and listed questions on which it sought FDA input. (Id. at 261.0002–.0003.)

Those listed Helsinn questions and the FDA answers, as set forth in the minutes, referred to two proposed Phase III clinical trials named PALO-99-03 and PALO-99-04 that would assess CINV in "moderately emetogenic" chemotherapy. They also referred to the fact that for all Phase III trials, Helsinn's proposed doses were 3 and 10 micrograms per kilogram (i.e., equivalent to 0.25 and 0.75 mg, see n. 11 supra). (Id. at 261.0007–.0008.) There were also proposed trials named PALO-99-

[19] Two of the consultants listed in the FDA March 10, 1999 meeting minutes were a representative of August Consulting, and a representative of Oread, Inc. (PTX-261.0001.) As Dr. Calderari testified, Helsinn as a foreign corporation was required to communicate and file documents with FDA through an FDA-recognized U.S. representative, and that was the function of August Consulting. (See dkt. 320 at 139.) The Oread representative was present pursuant to the July 1998 Development and Manufacturing Agreement between Helsinn and Oread that Dr. Calderari described in his testimony. See Section I.C.4.

05 and PALO-99-06 discussed in the minutes, as more particularly explained below.

The FDA in that meeting, as reflected in the minutes, was adamant that the Phase II study 2330, although named a "dose-ranging, efficacy . . . study," had not produced sufficient data to establish what the minimum effective dose of palonosetron in an intravenous pharmaceutical formulation for CINV would be. In the Background section of the minutes, discussing the 2330 study, the FDA stated:

> **Study 2330** was a single-dose, double-blind, parallel, multi-center dose-ranging study in which 161 patients (129 males, 32 females) were randomized to 0.3, 1, 3, 10, 30 or 90 mcg/kg of palonosetron. According to the firm, the objective was to determine dose-response over a wide range of palonosetron doses, using the low-dose levels of palonosetron for control. The primary efficacy measure was the proportion of patients with no emetic episodes and no rescue medication. When compared to the lowest doses (0.3 and 1 mcg/kg) only the 30 mcg/kg dose was statistically significant; a significant dose response trend was not evident.

(PTX-261.0002.)

This FDA minutes statement was referring to the fact that as reported in the 2330 study, at the 3 and 10 mcg/kg levels (equivalent to the 0.25 mg and 0.75 mg dosages that Helsinn ultimately proposed and selected for its Phase III trials), there was no statistical significance to any of the efficacy data in that study. Indeed, according to the FDA at that meeting, the only statistically significant dose level indicating efficacy in the 2330 study for CINV (using a

highly emetogenic chemotherapy agent) was 30 mcg/kg, or ten times higher than the 3 mcg/kg dose.

Additional statements in the FDA minutes of the March 10, 1999 meeting emphasized that determining the dose-related efficacy of the proposed palonosetron pharmaceutical formulations would have to abide the results of the Phase III trials. Here are some of those question and answer exchanges:

Clinical -- Question 5

Are the two trials presented in moderate dose CINV [referring to PALO-99-03 and PALO-99-04], with repeat cycle and pediatric data, considered sufficient to support the label claim, "Prevention of nausea and vomiting associated with initial and repeat courses of emetic cancer chemotherapy"?

- **This question is premature. The program appears adequate, however, all regulatory decisions, including any labeling claims, will be data driven. (Division representatives also noted that a dose response was not shown in Phase II Study 2330, and therefore it is questionable whether the appropriate palonosetron dose has been identified.)**

Clinical -- Question 6

Is [Phase II study] 2330 sufficient to support the label claim "Including high dose cisplatin"? Should a historical control analysis be conducted?

Note: In the question above, the firm appears to have written "high dose cisplatin" when "highly

> **emetogenic chemotherapy" is what was intended . . . .**
>
> - **Due to the lack of a dose response in this study, these data are inadequate to serve as pivotal efficacy support (although they may be useful as supportive data).**
>
> **(After discussion with the firm, it was agreed that the results of Study 2330 versus a historical control, along with another study in which two doses of palonosetron are compared to ondansetron, then validated by comparison to a historical control could be used to support a claim for palonosetron in the prevention of nausea and vomiting due to highly emetogenic chemotherapy. Note: Any regulatory decisions will be data driven.)**

(PTX-261.0005–.0006 (emphasis in original; bracketed text added).)[20]

Similarly, in commenting on the "protocol summaries" Helsinn had submitted before the meeting, with respect to proposed PALO-99-03 and PALO-99-04 trials involving

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[20] As referred to in this quoted text, and as seen in the later-submitted FDA filings, Helsinn was permitted to proceed with just one full-scale Phase III study for the highly emetogenic CINV ("HEC") efficacy, which was PALO-99-05. Helsinn was permitted to submit the re-analyzed results of study 2330, designated PALO-00-01, as the "supportive data" accompanying the PALO-99-05 HEC clinical trial. (See dkt. 322 at 108–26, 134.) Therefore, Helsinn was not required to conduct what would have been PALO-99-06, a second full-scale Phase III clinical trial for HEC efficacy. See n. 22 infra.

moderately emetogenic chemotherapy, the FDA advised Helsinn:

> **Efficacy data for Study 2330 show that results for the 0.3-1 mcg/kg doses did not differ significantly from the proposed Phase III doses (3 and 10 mcg/kg). Consider including the lower dose as an arm in the Phase III study.**

(Id. at .0008.)

The minutes of the March 10, 1999 FDA meeting also addressed, among other topics, the manufacturing of future commercial batches. The FDA had been made aware that Helsinn proposed to use the Syntex-manufactured palonosetron API in making the pharmaceutical formulations to be used in the Phase III trials, and the FDA expressed concern that for commercialization, the age of that API substance would be problematical. Helsinn replied that they did not plan to use any of that Syntex-made API in manufacturing the commercial batches. The FDA accepted that representation, but made it clear that it would require full disclosure of the planned commercial manufacturing arrangements, as well as commercial product stability data, before it would consider approving a New Drug Application for commercialization of any such product. (See id.) That portion of the minutes stated:

> - **We note your plan to use drug substance manufactured by Syntex (date of manufacture: 1995) for your Phase III drug product. The age of that drug substance is a potential problem.**
>
> **(Note: In response to this comment, the sponsor's representatives indicated that they plan to change**

> **the drug substance manufacturer prior to submission of an NDA; Helsinn-manufactured drug substance will be incorporated into the drug product planned for commercial use. The Division's chemistry representative indicated that the information to support this change should be presented clearly and completely in the NDA. He said the Helsinn drug substance manufacturing facility(ies) should be prepared to host an inspection at the time of NDA submission. He also said that three batches of drug product manufactured with Helsinn drug substance should be put on stability; at least one of those batches should be commercial scale.)**

(Id. at .0003.)

Dr. Calderari testified that the Helsinn development team continued to debate internally the questions of what dosage and concentration level or levels to select for the Phase III protocols during this time period. The Helsinn group at that time recognized the fact that the Syntex scientists, at the end of their Phase II work, had recommended a single 1.0 milligram dose for Phase III CINV testing. They were also acutely aware that the FDA said the Phase II 2330 study did not contain reliable dose-related efficacy data. On the dosage issue, when asked how Helsinn ultimately decided to take the two doses that it did select into the Phase III trials, he stated:

> It was . . . a big debate. I mean, generally speaking, you tend to run Phase III only with one dose, but as we have seen . . . , the FDA was concerned about not having shown this dose efficacy relationship, so our scientists suggested that we should run the Phase III

> with multiple doses, and I recall that we had a long discussion because Dr. Macciocchi wanted even to have a third dose, much higher. Then at the end, we came to a compromise to use these two doses, and this what then was proposed to the FDA in the end of Phase II [March 10, 1999] meeting.

(Dkt. 322 at 119 (bracketed text added).)[21]

Dr. Calderari also explained that the stability issue was also in the forefront of Helsinn's considerations at that time. Although Syntex had recommended a formulation containing 0.4 milligrams of palonosetron per milliliter of solution for a CINV product, there was a concern about stability of the product at that concentration. The Syntex internal documents had identified that "the higher the drug concentration in the solution, the less stable it becomes." (Dkt. 322 at 113, referring to DTX-0254 at 27.) The Syntex inventor Dr. Malefyt, in his September 14, 1998 consulting report to Helsinn, had similarly advised:

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[21] The March 10, 1999 FDA meeting minutes indicate that at that time, Helsinn had submitted only "protocol summaries" rather than completed proposed testing protocols, and that the doses being proposed at that meeting were expressed in micrograms per kilogram of patient body weight, specifically 3 and 10 mcg/kg. (See PTX-261.0007, .0008.) As discussed below in this Section, when Helsinn submitted its formal proposed Phase III protocols in April 2000, it had decided to simplify the protocols by specifying dosage in fixed-dose milligrams, rather than in relative micrograms per kilograms of patient weight, thus proposing 0.25 and 0.75 mg doses for Phase III. Throughout the trial evidence, including testimony by the parties' experts, those two different measurement forms were discussed in their equivalent values. Thus the parties recognized, for example, that 3 mcg/kg is equivalent to 0.25 mg. (See, e.g., dkt. 322 at 121.)

> The [P]hase [I and II] IV product required refrigeration. Stability is inversely related to [palonosetron] concentration apparently in both solid and liquid forms. If doses around 10 mcg/kg are required to obtain efficacy for CINV and PONV (both IV or oral liquid capsules), it will be challenging to formulate an IV and oral dosage form that provides sufficient mcg dosage to provide efficacy and also be sufficiently stable.

(PTX-245.0005 (bracketed text added).)

Dr. Calderari summed up the problem facing Helsinn in trying to achieve a balance between efficacy and stability in creating a Phase III formulation as follows:

> So at the end, this is the dilemma we lived from the -- .... So the dilemma was, me, as a chemist, I wanted -- or my team wanted -- a diluted as much solution, so less concentration (to make sure that at the end we would have had a product that would have been shelf stable), but of course the clinician wanted to use a dosage that was sufficient[ly] high to meet the requirement to treat emesis.

(Dkt. 322 at 117–18 (bracketed text added).)

6. Phase III protocol

Ultimately, Helsinn decided that to balance the documented concerns about efficacy and stability, it would take two different dosages and concentration levels into its Phase III trials for CINV. (See id. at 119.) On April 7, 2000, it submitted to the FDA a set of "safety and efficacy protocols" for Phase III clinical testing designated as follows:

- PALO-99-03 entitled, "A Double Blind Clinical Study to Compare Single IV Doses of Palonosetron, 0.25 or 0.75 mg and Ondansetron, 32 mg IV, in the Prevention of Moderately Emetogenic Chemotherapy-Induced Nausea and Vomiting"

- PALO-99-04 entitled, "A Double Blind Clinical Study to Compare Single IV Doses of Palonosetron, 0.25 or 0.75 mg and Dolasetron, 100 mg IV, in the Prevention of Moderately Emetogenic Chemotherapy-Induced Nausea and Vomiting"

- PALO-99-05, entitled "A Double Blind Clinical Study to Compare Single IV doses of Palonosetron, 0.25 or 0.75 mg and Ondansetron, 32 mg IV, in the Prevention of Highly Emetogenic Chemotherapy-Induced Nausea and Vomiting"

(DTX-0293-0001.)[22]

As shown in these protocol titles, all three protocols specified using both 0.25 and 0.75 mg doses of palonosetron. The 99-03 and 99-04 studies were directed to moderately emetic CINV ("MEC"), and the 99-05 study was directed to highly emetogenic CINV ("HEC"). The protocols specified that the selected concentrations of palonosetron API in the formulations for all three studies would be 0.05 mg/ml for the 0.25 mg dosage and 0.15 mg/ml for the 0.75 mg dosage. (See dkt. 322 at 108.) These concentrations were sharply lower than the 0.4 mg/ml that Syntex had recommended for the CINV formula. (See id.) The

[22] No PALO-99-06 study was needed, based upon the fact that the FDA allowed Helsinn to re-analyze the results of Phase II study 2330, designate that report as PALO-00-01, and submit it as support for the PALO-99-05 Phase III results. (See n. 20 supra; PTX-182.)

low concentrations were reflective of the goal, as described by Dr. Calderari, to promote stability by decreasing the concentration of palonosetron in the pharmaceutical formulation. (See id. at 113.)

Dr. Calderari was asked why Helsinn chose to bring two doses into each of those Phase III CINV trials, both of which were lower than the 1.0 mg dose for CINV that had been recommended by Syntex. (See id. at 120.) He said, "this was this compromise between increasing the chances of having a stable product from one side, and increasing the chances to have an efficacious product on the other side." (Id.) He explained that the risk that Helsinn took in selecting those relatively low doses for CINV was "that at the end, we would end up with a product that was not efficacious enough." (Id.)

Dr. Calderari testified, under questioning by counsel for Helsinn, that Helsinn did not know whether these lower doses would work for CINV efficacy, prior to receiving the results of the Phase III trials. He stated the reason was "[b]ecause it was not tested before, and during the Phase III trial, you have absolutely no idea how the clinical trial is going in terms of results." (Id. at 120–21.)

Helsinn itself made an apparently contrary statement, however, in its proposed Protocol No. PALO-99-03, dated November 15, 1999. There, referring to the table of data in the Phase II 2330 study summarizing patients' responses for CINV treatment with doses from 0.3/1 mcg/km to 90 mcg/kg, Helsinn stated, "Data from this study clearly demonstrate that the 3 μg/kg dose of palonosetron is the minimal effective dose in preventing CINV." (DTX-0293-0035.)

Chronologically, that statement was dated in late 1999 and submitted to the FDA in April 2000, despite the FDA's statements to Helsinn in the March 10, 1999 meeting minutes, that "a dose response was not shown in the Phase II Study 2330," and that "only the 30 mcg/kg dose was statistically significant; a significant dose response trend was not evident." (PTX-261.0001, .0005). When queried about it by counsel for Teva, Dr. Calderari testified as follows:

> Q. . . . . The term "minimal effective dose" is particularly important, isn't it?
>
> A. Well, I am not a medical doctor, but this is standard. I mean, if you want to go to a Phase III clinical trials, it's a fact that you have to have shown some efficacy in Phase II. Otherwise, you cannot jump and you will even not get the approval to go to the Phase III. So, yes, the product was showing some efficacy clearly.
>
> Q. Exactly. In real human beings.
>
> A. Yes.
>
> Q. And efficacy meaning it reduced the likelihood of CINV.
>
> A. Right. It was giving enough signal for us to take the risk to continue to the Phase III and getting approval from the FDA to move to the Phase III and show if we were really able to show a real efficacy to get an approval by the FDA, but this is standard. You finish the Phase II. You see a some signal. You go with the agency. You discuss, and then if everything is fine, you move to the next step.

(Dkt. 320 at 142–43.)

His testimony on this point was consistent, however, with the actual statements made by Syntex in the 2330 study Final Report, quoted in full in Section I.C.2, where Syntex reported, "**A statistically supported dose-response relationship for efficacy . . . between the lowest dose level of RS-25259 and each subsequent higher dose level was not observed in this study . . . .** Although no placebo control was incorporated into the design of this study, there **appeared to be** a step up in efficacy from the combined 0.3–1 μg/kg dose group to doses of 3 μg/kg and more . . . . **Based on the results of this study, a dose of 3 μg/kg or 10 μg/kg might be appropriate for further development.**" (DTX-0227-0015, -0016 (emphasis added).) This testimony was also consistent with what the FDA had informed Helsinn at the March 10, 1999 meeting, "**Efficacy data for Study 2330 show that results for the 0.3-1 mcg/kg doses did not differ significantly from the proposed Phase III doses (3 and 10 mcg/kg).**" (PTX-261.0008.) "[A] **dose response was not shown in Phase II Study 2330, and therefore it is questionable whether the appropriate palonosetron dose has been identified.**" (Id. at .0005.)

Following the March 10, 1999 FDA meeting, Helsinn continued its preparations to file proposed Phase III protocols with the FDA. The documentary evidence described below shows that as of March 24, 1999, Helsinn had already completed developing, on paper and in actual solution, the 0.05 mg/ml palonosetron concentration, with all measured excipients, that had been described in the Syntex formulation books and was later claimed in the '724, '725, and '424 patents. (The same 0.05 mg/ml palono-

setron concentration (with excipient content) was also reflected in the later-issued '219 patent, as the result of dose 0.25 mg palonosetron in 5 ml solution.) (See dkt. 320 at 175–76.)

Dr. Calderari testified that Example 4 in the written description of all four patents-in-suit is an intravenous formulation description that appeared in the Syntex formulation book. (Id. at 152.) Example 4 is reproduced in the margin.[23]

That same formulation, described in the Syntex research materials, had actually been made up into a bulk batch by Helsinn's contractor, Oread, before March 24, 1999. (See, e.g., DTX-1125-0001 to -0006.) This fact was reflected in statutory declarations with supporting documentation later filed in the USPTO during the prosecution of the patents-in-suit and related patent applications. One such example, under the application that led to issu-

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[23] Formulation I

The following is a representative pharmaceutical formulation containing palonosetron that is useful for intravenous formulations, or other liquid formulations of the drug.

Ingredient	mg/mL
Palonosetron Hydrochloride	0.05*
Mannitol	41.5
EDTA	0.5
Trisodium citrate	3.7
Citric acid	1.56
WFJ [water for injection]	q.s. to 1 ml
Sodium hydroxide solution and/or Hydrochloric acid solution	pH 5.0 + 0.5

*calculated as a free base

('724 patent, col. 7, lines 47–66 (bracketed text added).)

ance of the '724 patent, was a declaration of named inventors Calderari, Bonadeo, Cannella, and Enrico and Riccardo Braglia dated November 21, 2007. (DTX-0004-0001 to -0005; see also DTX-1125, a similar Bonadeo declaration dated Feb. 13, 2007, containing the two-page Exhibit A documents referred to in this series of declarations.)[24] That declaration stated, inter alia, as follows:

> 5) This patent application is based on the discovery of liquid formulations of palonosetron with improved stability.
>
> 6) The formulations can be stored for prolonged periods of time in a variety of conditions without significant degradation or loss of potency, and thus are considered pharmaceutically stable.
>
> 7) The formulations were developed by us at Helsinn in the late 1990s, and were completed sometime before March 24, 1999.
>
> ....

[24] During the prosecution of the USPTO applications that led to issuance of the '724, '725, and '424 patents, Helsinn submitted declarations signed by named inventors Dr. Calderari, Daniele Bonadeo, Roberta Cannella, and Enrico and Riccardo Braglia (the names of the latter two Helsinn executives were subsequently deleted as inventors per U.S. inventorship requirements). There were several such applications in the patent family history, and those declarations were similar in content but filed under various patent application numbers. (See generally dkt. 289 (chart: Family Tree of Patents at Issue).) Examples of those declarations are in evidence as DTX-0004, DTX-0287-0413, and DTX-1125.

14) The Example 4 formulation was developed by us sometime before March 24, 1999 and transmitted to a contract manufacturer for Helsinn, Oread Laboratories in Palo Alto California ("Oread") for the production of commercial scale batches of palonosetron hydrochloride.

15) A copy of the master batch record developed by Oread for the formulation is contained in Exhibit A hereto.

16) The master batch record describes the Example 4 formulation . . . .

17) As can be seen, the batch record has an effective date of March 24, 1999, and thus makes clear that we developed the formulation before this date.

18) In fact, we had invented and were in possession of all of the subject matter currently claimed in . . . [the applications for the '724, '725, and '424 patents] as of March 24, 1999, because we had completed stability studies for the Example 4 formulation, and understood the effect that variations in palonosetron concentration, pH, and excipient concentrations would have on the stability of the formulation.

(DTX-0004-0001 to -0003 (bracketed text added).)

Dr. Calderari described that when he took over the role for the development of palonosetron at Helsinn, he had to read a variety of results from Syntex. He said that Syntex's formulation book, describing various formulations including Formulation 4, was "where they describe

their attempt, their experiment to arrive to a formulation that might be suitable for clinical trial and then after for commercialization. But to my surprise, when I made the first due diligence, they had never manufactured that formulation, that they had absolutely no . . . data about the stability of potential formulation to be used in a clinical trial." (Dkt. 320 at 116.) Furthermore, he stated that the Example 4 concentration formulation of 0.05 mg/ml was recommended by Syntex to be used in Phase III clinical trials for PONV efficacy (then called "Formulation 90"). (Id. at 116–17.) On the other hand, Syntex had recommended a Phase III palonosetron concentration formulation of 0.4 mg/ml for CINV efficacy (then called "Formulation 89"). (Dkt. 322 at 111–12.)

Dr. Calderari also testified that as to the written description of the Example 4 formulation, as embodied in the actual developmental formulation batches prepared by Oread, the inventor statement that he and the other inventor declarants signed, that "the formulations . . . were completed sometime before March 24, 1999," was a true statement. (Dkt. 320 at 149.)[25] He stated, "[e]xactly, and this is exactly what we have completed at that time. We have completed the selection of the formulation that we will then go and test for stability and for the clinical trial. This is what we had completed at that time." (Id. at 150–51.) He had the same answer regarding the statement at the end of the inventor declaration, "we had invented and were in possession of all of the subject matter

[25] The other inventor declarants, Dr. Bonadeo, Dr. Cannella, and Dr. Braglia, all testified consistently that the statement made regarding the Example 4 formulation was true at the time that they signed the declaration. (See dkt. 330 at 22–23, 41–42, 66.) None of the inventor declarants sought to add any testimony beyond their prior recollection. (See id.)

currently claimed." (DTX-0004-0003.) In his words, "we [had] completed the specification, the selection of this formulation to then be tested in stability studies and in human beings." (Dkt. 320 at 155.)

Helsinn's decision to proceed to CINV Phase III clinical trials with fixed doses of 0.25 mg and 0.75 mg in 5 ml vials was made following the March 10, 1999 FDA meeting (in which a range of doses was discussed, in the weight-based measurements (mcg/kg) used in the Phase II studies), as reflected in the Phase III protocols subsequently submitted to the FDA. (See, e.g., DTX-0293-0001; dkt. 322 at 132.) Dr. Calderari testified that as part of those dosage selections for Phase III, Helsinn decided on corresponding palonosetron concentrations of 0.05 mg/ml and 0.15 mg/ml, which were both lower than the 0.4 mg/ml concentration that Syntex had recommended for CINV Phase III trials. (Dkt. 322 at 108.)

While Helsinn was preparing to submit its completed Phase III safety and efficacy protocols to the FDA, which occurred on April 7, 2000 as described below, Helsinn was communicating with the FDA regarding stability testing of the development formulation lots that Oread had prepared (in the selected palonosetron doses of 0.25 mg and 0.75 mg and concentrations of 0.05 mg/ml and 0.15 mg/ml). A letter from Helsinn to the FDA dated August 19, 1999 stated: "Six month stability data for development lots indicate that the Phase 3 formulation is expected to remain stable for a minimum of 18 months, when stored at 25 °C and protected from light. We commit to monitor stability of the clinical material and to resupply the drug product as appropriate, to ensure that the clinical material has the identity, quality and purity it purports to have." (DTX-0999-0002.) Dr. Calderari said this was "the formulation

we pick[ed] up and we improved, we optimized, and we ran at Oread, and by the time we made the submission, we have six months' stability data." (Dkt. 322 at 163.)

The formal Phase III safety and efficacy protocols for PALO-99-03 and PALO-9904 (two MEC studies) and PALO-99-05 (one HEC study) were submitted to the FDA by letter dated April 7, 2000, under the existing IND number 39,797. (DTX-0293.) At that time, Oread was still performing its contractual functions in support of the trials. For example, a memo from Oread to Helsinn dated April 10, 2000 described "two phase 3 clinical lots" manufactured by Oread in March and April 1999, containing either 0.05 mg/ml or 0.15 mg/ml palonosetron, in 5 ml glass vials according to the Phase III specifications. It reported chemical and physical stability based on up to 6 months of available data, and "[t]he stability monitoring of these two clinical lots is continuing according to the protocol." (DTX-1027-0038.) Dr. Calderari confirmed that Oread did provide clinical supplies of the formulation that is covered by the patents-in-suit for Helsinn, in preparation for conducting the Phase III trials, and Helsinn paid Oread for those batches. (Dkt. 320 at 179–82.)

The INTRODUCTION section of the formal Protocols for all three Phase III clinical studies, PALO-99-03, PALO-99-04, and PALO-99-05, contained the following types of statements:

> Results achieved in Phase II CINV studies suggest that palonosetron is safe and effective in preventing nausea and vomiting following emetogenic chemotherapy, especially during the first 24 hours after administration.

> Given the high affinity of palonosetron for the 5-HT3 receptor and efficacy results in both animal models and in Phase II studies, a single dose of palonosetron is expected to control acute CINV following moderately and highly emetogenic chemotherapy. Furthermore, due to the long half-life of palonosetron in humans, a single dose of palonosetron may also be beneficial in controlling the delayed phase (24-120 hours) of nausea and vomiting induced by a chemotherapeutic regimen. This study is designed to support the hypotheses that palonosetron is not inferior to currently available 5-HT3 receptor antagonists and is effective in preventing nausea and vomiting following moderately emetogenic chemotherapy. . . .

(See DTX-0293-0030 (PALO-99-03); see also id. at -0149 (PALO-99-04); id. at -0257 (PALO-99-05, replacing "moderately emetogenic" with "highly emetogenic").)

7. Commencement of Phase III trials

All three Phase III clinical trials were performed by a German contract research organization named Kendle GmbH & Co. ("Kendle"). (See DTX-0293-0001 to -0007; DTX-0288-0003; dkt. 322 at 54.) The April 7, 2000 protocol application specified that the "name and title of the person responsible for monitoring the conduct and progress of the clinical investigations" was Alberto Macciocchi, MD, Senior Manager, Product Development at Helsinn. (DTX-0293-0004.) Dr. Macciocchi was still in that position as of July 19, 2002, the date of the Clinical Study Report for the earliest-completed trial, PALO-99-03. (DTX-0288-0003 to -0004.) See n. 16 supra.

The patient participation in the three Phase III clinical trials began with the earliest of those trials,

PALO-99-03. According to the Clinical Study Report at the end of that trial, the Study Initiation Date ("first patient in date") for PALO-99-03 was August 1, 2000. The Study Completion Date ("last patient out date") for that trial was October 2, 2001. (Id. at -0003.) Neither of the other two Phase III trials had a data "locked" date prior to the critical date of January 30, 2002. See Section I.C.11. Therefore, much of the evidence in this chronology focused on the progress of PALO-99-03.

In September 2000, just as the first of the three Phase III clinical trials began, Helsinn issued a press release entitled "Helsinn Announces That Patient Enrollment For Phase III Palonosetron Trials Progresses Both in the USA and Europe." (DTX-1227-0001.) That publication stated, inter alia:

> "The Phase II trials demonstrated the efficacy of Palonosetron in the prevention of emesis with no significant side effects . . . ," said Luigi Baroni M.D., Director of Scientific Affairs. "We are now eager to complete the data necessary for NDA filing scheduled for early 2002."

(Id.)[26]

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[26] The September 14, 2000 Helsinn press release also stated: "'Upon market approval, Helsinn will be in a position to supply its marketing partners with a finished product ready for distribution,' said Giorgio Calderari, Director of Technical Affairs. Helsinn is seeking marketing partners for this patented product in different territories." (DTX-1227-0001.) The reference to "seeking marketing partners" is a topic covered in the trial evidence in some detail, as discussed in Section I.C.9. The words "patented product" appear to relate, at least in the United States, to the original '333 genus patent on the palonosetron molecule, which would not expire until 2015.

8. The SP agreements

Returning to the topic of contracting, it will be recalled that Oread had suddenly closed down in or about June 2000, just before the Study Initiation Date for PALO-99-03, and with the other two Phase III clinical trials gearing up as well. As a result, Helsinn needed to find another organization to pick up Oread's functions and move forward with it in the development project. Dr. Calderari testified that Helsinn then hired SP Pharmaceuticals L.L.C. ("SP"), "essentially, . . . to finish the work that we started with Oread . . . ." (Dkt. 320 at 196.)

A document later submitted to the FDA as part of Helsinn's NDA filing summarized that portion of the drug product development history as follows:

> Oread . . . was selected as the manufacturing site for the formulation of the injectable solution for Phase 3 clinical supplies and for the manufacturing of commercial batches (reference IND amendment serial #064, 19 August 1999). A Commercialization Development Plan was agreed with the Agency during the End of Phase 2 Meeting, 10 March 99, and enacted to complete the transfer of the manufacturing technology for the optimized drug product formulation from Syntex to Oread, Inc.
>
> Due to the subsequent closure of the Oread manufacturing facility in June, 2000, SP Pharmaceuticals, Albuquerque, New Mexico, was selected as the site of manufacture for future NDA commercial drug product, as well as additional Phase 3 clinical batches. No significant changes in the manufacturing process or equipment occurred with the site transfer. Reference is made to IND Amendment Serial #95, 22 Nov. 2000,

> which was submitted in support of SP Pharmaceuticals as the site of manufacture for commercial product.

(DTX-0310-0005, -0006 (footnotes omitted).)[27]

Dr. Calderari stated that Helsinn's contractual relationship with Oread never advanced to the point of any serious negotiations or contracting regarding Oread as a manufacturer of any palonosetron commercial product (despite Helsinn's apparent designation of Oread to the FDA in March 1999 as the "selected" site for such manufacturing). (Dkt. 322 at 125–26.) Dr. Calderari characterized the Oread agreement as a "fee for service agreement." (Id. at 122.) Nevertheless, the above-quoted FDA filing statement indicates that during the Phase III process, Oread was at least identified by Helsinn to the FDA as the "selected" site for future commercial manufacturing.

The first agreement that Helsinn entered into with SP, even before Oread totally stopped functioning, was a Secrecy Agreement dated April 10, 2000. (PTX-361.) It was followed by a "Letter of Intent" designated "Confidential" ("SP Letter of Intent"). (DTX-0258-0002.) The SP Letter of Intent was signed by SP on October 19, 2000, and was signed by Dr. Calderari for Helsinn on November 7, 2000. (Id. at -0004.)

The SP Letter of Intent stated that the parties were "in the process of negotiating a Master Services Agreement for development or manufacture of pharmaceutical products," and they agreed that SP would begin such work, subject to the terms of the Letter of Intent and any

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[27] The Helsinn agreements with SP, referred to in this quoted FDA filing, are described below in this Section.

Scope of Work documents they would mutually agree to in writing. (Id. at -0002.) Attached to the Letter of Intent, signed by the parties on the same dates as the Letter of Intent itself, was a Scope of Work description (id. at -0006 to -0020), and an Appendix A: Pricing and Technology Transfer. (Id. at -0021 to -0023.)

The Scope of Work stated, among other things, that SP "will manufacture Product meeting the Specifications . . . and perform such other responsibilities detailed" therein. (Id. at -0006.) It described that Helsinn would "furnish SP with sufficiently tested and released API to guarantee filling the theoretical batch size. . . ." (Id.) It stated that SP would furnish the vials and the listed incipient raw materials (the EDTA, mannitol, citric acid, etc.), along with related documentation, and would "manufacture the product according to the approved master batch record." (Id. at -0010.) It also provided that SP would do specified quality testing on the finished products, described as 0.05 mg/ml and 0.15 mg/ml (id. at -0012, -0013), and would do stability testing on "Product: Palonosetron-HCl IV injection 0.25 mg/vial & 0.75 mg/vial." (Id. at -0013, -0014.) Among other provisions, it also stated:

> **J. Commercial Product Validation**. SP will perform the following process validation, manufacturing and stability activities to prepare for product commercialization.
>
> 1. Manufacture 3 lots of up to 50,000 vials of Palonosetron-HCl intravenous injection for commercial product validation and sale.
>
> . . . .

2. Perform stability studies on the commercial product validation lots.

. . . .

(Id. at -0015.) There was also an Appendix A: Pricing and Technology Transfer, describing some batches that were going to be manufactured by SP and a price for those batches, including "[m]anufacture up to 10,000 vials of the . . . finished drug product." (Id. at -0021, -0022.)

Dr. Calderari testified that the SP Letter of Intent and attached Scope of Work document did not actually provide for SP to manufacture any commercial product for Helsinn. (Dkt. 322 at 129.) He explained that it provided that Helsinn would pay SP for each activity mentioned in the Scope of Work, including to manufacture the batch size Helsinn was requiring them to manufacture at the time. (Id.) He said that the purpose of the SP Letter of Intent was "a development agreement to make some batches, to test them, to put on stability, and possibly to use in clinical trials." (Dkt. 320 at 196.) He confirmed that SP did actually do the work of creating development batch lots and clinical lots under the SP Letter of Intent. (Id.)

Dr. Calderari said that it was only after the critical date, on June 24, 2002, that Helsinn and SP entered into an agreement for future commercial manufacturing. (Dkt. 322 at 129.) That agreement is identified in the margin.[28]

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[28] On June 24, 2002, a formal Development and Manufacturing Agreement was entered into between SP and the Helsinn subsidiary in Ireland, Helsinn Birex Pharmaceuticals Ltd. (DTX-0259.) That Agreement also contained confidentiality provisions. (Id. at -0024, -0025). At that time, any FDA approval of a Helsinn palonosetron product was still in the future, but this Agreement set the

It is undisputed, however, that as part of its eventual NDA filing, Helsinn recounted that as of November 22, 2000, Helsinn had filed an amendment to its Phase III IND application informing the FDA that "SP Pharmaceuticals, Albuquerque, New Mexico, was selected as the site of manufacture for future NDA commercial drug product, as well as additional Phase 3 clinical batches." (DTX-0310-0006.) See n. 27 supra and accompanying text. The NDA contained, as required, detailed descriptions of the "Selected Manufacturing Process" that SP would perform to make the proposed commercial product, as well as an explanation of the differences between that commercial process and the manufacturing processes SP would use to make "registration batches," that is, clinical trial formulations. (See DTX-0310-0241 to -0243.)

Dr. Calderari explained that as part of the Phase III clinical trial process, the FDA required Helsinn to show three batches of product formulation manufactured at the intended site of commercialization, tested for at least 12 months of stability. He said the FDA would not consider the Oread stability data for that purpose because Oread was no longer the intended site of commercialization. Therefore, the FDA required three batches made at the SP site to be tested for stability, to demonstrate quality control at the SP plant before Helsinn could submit an NDA application. He recalled that process was accomplished using SP, at its manufacturing site, and Helsinn had that stability data available in approximately the second half of 2002. (Dkt. 322 at 155–56.)

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terms for that eventuality. (See id. at -0003, defining "Commercial Product" as "the Product once it has been approved by a Health Authority for commercial marketing in a Territory.")

9. The MGI Agreements

The topic of contracting continued to be a feature of Helsinn's drug product development process after the first of the Phase III clinical trials began on August 1, 2000. Having secured, on a confidential basis, the assistance of first Oread and then SP for the functions those companies performed, Helsinn was also simultaneously in search of "marketing partners," as announced in its September 14, 2000 press release. See n. 26 supra.

Riccardo Braglia, who succeeded his father as CEO of the Helsinn companies, testified (in deposition excerpts in evidence) that their business model is "to licensing-in, develop, and licensing-out." (Dkt. 330 at 54.) He said "we are looking to opportunities of product which are in the . . . early stage of development or middle stage of development, and also are good opportunities." (Id.)

He mentioned two goals of the licensing-out efforts for the palonosetron project: first, to bring in license fees and thus minimize financial risk of such huge investments for Helsinn, and second, to plan for marketing and distribution of product in the United States after FDA approval. (Id. at 54–64.) He said that the "commercial partner" agreement that Helsinn normally did with its partners around the world would feature an up-front payment to Helsinn when the agreement was signed, as well as "milestone" payments (also to Helsinn) at certain points in the development or filing or approval of certain products. (Id. at 57.) He added that for the palonosetron project, as Helsinn discovered the process was much more costly than anticipated, "the strategy was to find as soon as possible a partner that will give us some milestones [i.e., milestone

payments] for the . . . licensing rights to the U.S. market." (Id. (bracketed text added).)

Helsinn conducted a lengthy and arduous search for a willing "commercial partner" for the U.S. market, described by Helsinn employee Dr. Rachid Benhamza at trial, which resulted in written agreements with MGI Pharma, Inc. ("MGI"), a Minnesota company. (Id. at 82-149.) Those agreements, both effective on April 6, 2001, were a License Agreement between MGI and Helsinn (DTX-0115) ("MGI License Agreement"), and a Supply and Purchase Agreement between MGI and Helsinn Birex, the Irish subsidiary. (DTX-0261 and DTX-0311 (same) ("MGI Supply Agreement").)[29]

Dr. Calderari, who participated in negotiating those agreements, described the general nature of the License Agreement as follows:

> [I]t's our standard practice that we grant the rights to a company to explore a patent, and with this, they pay us some licensing fees, and they then will pay us for future royalties on the sales. Concomitant, but subject to this licensing agreement, we also make a supply and purchase agreement that we set the stage for future supplies, once we arrive to get an approval, and also there the price is subject to the price that the company will achieve selling the product on the market. Now, of course, if the license agreement is not there because

[29] The MGI License Agreement recited that the parties had entered into a Secrecy Agreement on May 25, 2000, and a Letter of Intent on October 5, 2000, under which they had exchanged confidential information and performed due diligence. (DTX-0115-0004.)

> the product would have been unsuccessful in Phase III, then the supply agreement would not be there.
>
> . . . .
>
> [F]or MGI, it was quite clear that this was a developmental . . . . product, so they were not buying a product. They were buying the rights to participate in the development effort to potentially have a product in the future.
>
> . . . .
>
> They paid licensing fees for the licensing agreement, for granting the right, for entering in the agreement. . . . And that helped to continue . . . the clinical trials, because we were still doing the clinical trials. . . .

(Dkt. 320 at 212-14.)

His testimony about the nature of the MGI Supply Agreement, under questioning by counsel for Teva, stated in pertinent part:

> Q. Let's go . . . to the Supply and Purchase Agreement, DTX-0311 . . . . So here we're talking about purchasing products; is that right?
>
> A. Yes. This would set the stage of future purchase of product in the event that we would get to an approval of one or the other, if any, of the formulations that we were studying in the clinical trials.
>
> . . . .

Q. . . . . It says, in 2.1, "Throughout the term of this agreement, . . . MGI undertakes to purchase exclusively from HBP" . . . . "and HBP undertakes to sell to MGI, MGI's entire requirements of the products to be distributed, promoted, marketed and sold by MGI or MGI's affiliates under the License Agreement." That's what the agreement was?

A. Yes. In case there would have been sales, then they would have to purchase from HBP.

. . . .

Q. [W]e just looked at IND 39,797, Amendment 64 . . . . And it set forth two . . . possibilities for a product, one of which was the formulation that is set forth in the patent in this case, is that right?

. . . .

A. In the IND 39,797, they will describe two products, 0.25 and 0.75 milligrams.

Q. And one of them, the .25, is the formulation that's contained in the patents that are at issue in the lawsuit; is that right?

A. Correct.

Q. . . . . it says that whatever will be the product that would be approved -- registration . . . means market approval -- then we will supply whatever will be the product that will be approved.

Q. Right. And it says what the current products are?

A. Yes. This is a description of the current product that were . . . in this Amendment, in the clinical trials.

Q. Which you're seeking approval on at the time you signed this agreement?

A. We were, but we were making the clinical trials, yes.

Q. And which you expected to get approval on?

A. Well, we had the hope. I mean –

Q. Well, you wouldn't have entered this agreement if you didn't expect to get approval, right?

A. No.

Q. And so the products, . . . if you look at Article 2.1, that's the definition of products, and then it says, "MGI undertakes to purchase exclusively from HBP,". . . and HBP undertakes to sell to MGI, "MGI's entire requirements of the products." That's what the agreement is about?

A. Yes. The product that would be approved, yes.

Q. And a price was agreed to, or a pricing scheme was agreed to with respect to these products? Isn't that correct?

A. Yes. . . . It was setting the stage for the future -- I mean, for regulating the purchase process when the product would have been approved, if approved.

(Dkt. 320 at 210–19.)

The definition of "Products," identical in form in the MGI License Agreement and the MGI Supply Agreement, stated:

> "Products" means the pharmaceutical preparations for human use in I.V. dosage form, containing the Compound as an active ingredient [referring to palonosetron hydrochloride] in the formulation which will be described in the Registration [defined as regulatory approval to market the Products]. The current formulation as submitted to the Food and Drug Administration . . . in the IND 39,797 Amendment #64 . . . is described in the [First Appendix of MGI Purchase Agreement; Third Appendix of MGI License Agreement] hereto.

(DTX-0115-0007 (License Agreement); DTX-0311-0006 (Supply Agreement) (bracketed text added).)

The Appendix referred to in the above-quoted definition, identical in both Agreements, read as follows:

> **THE PRODUCTS**
>
> Qualitative description of the Products as submitted to the United States Food and Drug Administration under IND 39,797 Amendment #64. . . .
>
> 1.Palonosetron HCl Intravenous injection is supplied as a sterile, isotonic solution in 5 ml Type I clear glass vials each containing 5 ml of product. The product is clear and colorless solution, and contains the equivalent of either 0.05 mg/mL or 0.15 mg/mL of Palono-

> setron free base. The formulation also contains mannitol as a tonicifying agent, edetate disodium as a chelating agent and citrate buffer to maintain the pH of the solution at the target pH of 5 (±0.5).
>
> 2. The product is terminally sterilized.

(DTX-0115 (License Agreement) at 84; DTX-0311 (Supply Agreement) at 28.)

Both Agreements also contained parallel and mutual confidentiality provisions, of which the following text is representative:

> MGI shall treat as strictly confidential, and shall use solely for the purpose of and in accordance with this Agreement, any and all information, data and/or document received hereunder . . . not generally known to the trade (all hereinafter referred to as the "Confidential Information"). MGI shall not make such Confidential Information available to any third Party, including any of its Affiliates, except to competent government agencies to which it will be necessary to disclose such information, and in this case (a) strictly to the extent requested by said agencies and (b) only upon exercise of its best efforts to cause said agencies to maintain confidentiality.

(DTX-0311 (Supply Agreement) at 18.)

MGI Pharma, Inc., is a publicly-traded company required to file SEC disclosures. A published SEC Form 8-K reported:

> On April 6, 2001, MGI PHARMA, INC. . . . announced that it had entered into definitive agreements with

> Helsinn . . . pursuant to which Helsinn granted to the Company exclusive license and distribution rights to the product candidate palonosetron in the United States. . . . Under the terms of the license agreement, the Company will make $11 million in initial payments, ... and will make additional payments to Helsinn based on the achievement of development milestones. The Company will also pay royalties to Helsinn based upon set sales. Under the terms of a related supply agreement, an affiliate of Helsinn will supply the Company's requirements of finished product. The Company will pay the affiliate product supply fees based upon net sales. The term of each of the agreements is ten years from the launch of the commercialized product, unless earlier terminated by the parties.

(DTX-0367-0002.)

Redacted copies of the MGI License Agreement and the MGI Supply Agreement were attached as exhibits to that Form 8-K report. The Appendix to each agreement that identified "**THE PRODUCTS**," quoted above, was not attached to that public filing. (DTX-0367 (passim).) What was attached as an exhibit to the MGI Form 8-K report, and incorporated into that Form 8-K report, was the press release dated April 10, 2001 announcing the execution of those agreements, quoted in the margin. (See DTX-0367-0002.) Neither the publicly disclosed MGI Form 8K documents nor the Helsinn/MGI April 10, 2001 press release disclosed the formulations being tested in the Phase III trials.[30]

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[30] The April 10, 2001 press release stated, inter alia,

10. Status of Phase III clinical trials on January 30, 2002

The designs of the three Phase III clinical trials were similar, with differences in the comparator drug (ondansetron in Studies 99-03 and 99-05; dolasetron in Study 99-04) and in the nature of emetogenic chemotherapy agent (moderately emetogenic in Studies 99-03 and 99-04; highly emetogenic in Study 99-05). (See DTX-02930001.) Each of those studies was designed with the two selected palonosetron dose levels of 0.25 mg or 0.75 mg. (Id.) The CRO responsible for the trials was identified as Kendle International Inc., with headquarters in Munich, Germany and Cincinnati, Ohio. (See, e.g., DTX-0293-0036.)

The Study Design section of the PALO-99-05 protocol, which was representative of the designs for the other two Phase III trials, summarized the design of that study as follows:

> **Palonosetron is a potent and selective 5-HT3 antagonist with an extended half-life, in Phase 3 development for the prevention of chemotherapy-induced nausea and vomiting** (CINV). Completion of Phase 3 trials could allow for NDA (New Drug Application) submission in the first half of 2002. When launched, palonosetron will compete in the $1 billion North American CINV market.
>
> . . . .
>
> Based on the extended half-life of palonosetron and the results of the Phase 2 trial, its efficacy will be assessed over Day 2 through Day 5 following treatment, in addition to the primary efficacy measure of complete response during the 24-hour period after the start of chemotherapy.

(DTX-1022-0002 (emphasis in original).)

> This is a multicenter, Phase III, randomized, balanced, controlled, doubleblind, double-dummy, parallel, stratified, and active comparator study design comparing the efficacy, safety and tolerability of single IV doses of palonosetron, 0.25 mg or 0.75 mg, with a single IV dose of ondansetron 32 mg, in the prevention of highly emetogenic chemotherapy-induced nausea and vomiting. The active comparator, ondansetron 32 mg, is the FDA-approved IV regimen for the prevention of nausea and vomiting following highly emetogenic chemotherapy. This dose is also used in Europe for the prevention of CINV. Implementation of published historical placebo controls will be used to validate the trial, demonstrating its sensitivity. It is anticipated that 80 investigative centers will participate in this study; 40 centers in Europe, 35 centers in the United States and 5 centers in Canada. The list of the investigative centers will be distributed to all parties involved in the trial.

(DTX-0293-0263.)

The first-completed Phase III trial was PALO-99-03, as previously stated, with a "last patient out" date of October 2, 2001. (DTX-0288-0003.) The "last patient out" date of PALO-99-04 was December 27, 2001. (DTX-0289-0002.) The "last patient out" date of PALO-99-05 was December 31, 2001. (DTX-0290-0002.)

The final reports of those studies, entitled "Clinical Study Reports," were all dated after January 30, 2002, as described below. See Section I.C.11. Contents of those final reports, however, gave information about the designs and procedures of the studies when the studies were approved by the FDA initially, and later amendments.

The Clinical Study report for PALO-99-03 stated that there were 571 patients enrolled, in 58 active testing centers: 16 centers in Germany, 10 in Italy, 2 in the United Kingdom, 7 in the Netherlands, and 23 centers in Russia, subdivided by region in Arkhangeisk, Moscow and St. Petersburg. (DTX-0288-0006.)[31]

The PALO-99-03 Clinical Study Report, in its Synopsis, also gave an overview of the statistical methods chosen to analyze the data generated in the clinical trials, as quoted in the margin.[32]

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[31] The comparable portion of the PALO-99-04 Clinical Study Report stated there were 592 patients enrolled, and 61 study centers in the United States and Mexico. (DTX-0289-0005.) Likewise, the PALO-99-05 Clinical Study Report said it had 680 patients enrolled, and 76 centers in Europe, Russia, United States/Canada, and Mexico. (DTX-0290-0005.)

[32] The PALO-99-03 Clinical Study Report contained a Synopsis that described the statistical methods used in analyzing the data, stating in part as follows:

> The primary efficacy variable was the proportion of patients considered to have achieved a complete response during the first 24 hours after administration of chemotherapy. The analysis based on the ITT cohort [563 patients] was considered as a primary analysis. To demonstrate the non-inferiority of at least 1 dose of palonosetron to ondansetron, the lower bound of the 97.5% confidence intervals (CI) for the difference (palonosetron minus ondansetron) between the proportion of patients with complete response (CR) during the first 24 hours after administration of chemotherapy was calculated and compared to the pre-set threshold (-15% difference). Moreover, to investigate the equivalence of the 2 palonosetron doses with respect to CR (0 to 24 hours) the bound of the two-sided 95% CI of the difference between the proportions of CR (0 to 24) were compared to the preset threshold (±15%). The validation/study sensitivity as as-

The evidence presented at trial established that the following sequence of events occurred during the period of time between the PALO-99-03 "last patient out" date, October 2, 2001, and the critical date (for on-sale bar purposes) of January 30, 2002.

An explanation of some of the PALO-99-03 documents was provided at trial by Helsinn expert witness Dr. Carl Peck. He is an M.D. with experience in internal medicine, pharmacokinetics and biostatistics, whose background included a six-year period as the director of the FDA's Center for Drug Evaluation and Research ("CDER"), the division with responsibility for all drug applications for human administration. He also has a current "special government employee" consulting status with the FDA. (Dkt. 337 at 4–16.)

Reviewing the PALO-99-03 files in evidence and the underlying documentation, Dr. Peck described the work that was done after the clinical study with patients closed on October 2, 2001. Here is his summary of the next few

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sessed by comparing CR (0 to 24 h) of the active control ondansetron with modeled historical placebo results and modeled historical ondansetron results from the literature. Complete response at further time points was analyzed using the same statistical methods as for the primary efficacy parameter. Complete control and the proportion of patients receiving rescue medication were analyzed using the Chi-square test. Furthermore, Poisson regression analysis was performed for the emetic episodes taking into account if rescue medication was administered. Quality of life, number of emetic episodes, severity of nausea and patient global satisfaction were compared between the treatment groups using the Kruskal-Wallis test or the Wilcoxon test.

(DTX-0288-0008 (bracketed text added).)

steps in the PALO-99-03 process after that "last patient out" date:

> There is no fully assembled, blinded or unblinded data set at that moment. That's a milestone in the execution of a clinical trial, and if you think about it in a multi-center, multi-national clinical trial, there's a lot to do with respect to gathering the data from each site, making sure that the data has been entered properly. In this case, I have read in the protocol that all the data was collected on handwritten case report forms, so those had to be translated into a computer. They used a double entry system, meaning that two independent persons take the data from the case report form and put it into the computer. Those have to be assembled in each center, then they have to be sent to the CRO, Kendle in this case in Munich, which will assemble them all, and then . . . begin to evaluate the quality. This is all well articulated in the protocol, because regulatory agencies and a POSA would require that if you're going to analyze the data for this purpose, it's got to be high quality. It's got to be verified. The company was even doing site visits during that period of time at some of the sites. In fact, one collection of sites was in Russia. One was up near the border of Siberia, and there was a site visit on that very site after the last patient out in order to validate that everything had been done right at that site.
>
> . . . .
>
> The CRO is doing this, although sometimes the company will commission an independent quality assurance company to do this as well. There were actually a handful of CROs that were working for Helsinn on contract, located in different countries, who were

> working on the whole execution and assembling of the data.
>
> . . . .
>
> What we see here or what we know about these three trials is that it took about eight weeks. That's most clearly shown in the study report for the 99-03 in which there's a meeting that's identified that happened on December 11th and 12th of 2002 [sic: 2001], in which the data quality committee got together to discuss all of the assembled data.
>
> . . . .
>
> [That] whole process is called blind data review, but the meeting in December, it was sort of the final summit meeting of the independent evaluators who were qualifying the data.

(Dkt. 337 at 65–67.)[33]

Dr. Peck testified that the two-day "blind review" meeting was conducted independent of Helsinn, and Helsinn did not participate in any of the blind data review. (Id. at 67–68.) Dr. Peck said that meeting resulted in a formal protocol amendment submitted to the FDA on December 13, 2001, revising the study groups that would be analyzed for efficacy, as described in the Final Study Report. (Id. at 67–68, 165–66.)

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[33] Dr. Peck stated that the PALO-99-03 blind review meeting was on December 11 and 12, 2002, as cited above. The meeting was actually on December 12 and 13, 2001. (See DTX-0288-0056.) He apparently misspoke the date, but the record is clear.

The PALO-99-03 records state that after the "blind review" meeting, the database was closed on December 19, 2001. (DTX-0288-0056.) Dr. Peck referred to that as when the data was "locked." (Dkt. 337 at 66.) Dr. Calderari testified that he did not see any of the blinded data results, and he did not know whether anyone else at Helsinn saw blinded results after the last patient out date of the PALO-99-03 study. (Dkt. 322 at 56–57 (bracketed text added).)

Dr. Peck was asked whether the clinical study data could change during the period immediately after the "last patient out" date. He said:

> [T]he raw data can change during that period of time, yes. Because if they discover a blunder, [if] they discover that the data was not legible, if they find that one of the patients actually got the wrong drug, there's a lot of things that can happen during the data quality evaluation that can lead to changing actually the raw data. It's only after the raw data have been qualified and the database locked, what they call locked -- and that's the point in time where they have decided that, yes, we've done all of the quality control . . . that we possibly can and we think this data is valid.

(Dkt. 337 at 66–67.)

The PALO-99-03 documents list January 2, 2002 as the "unblinding" date, which Dr. Peck said was the first date that the sponsor, Helsinn, would have been allowed to see the data. (Id. at 164–65; see DTX-0288-0056.) However, the data was only in preliminary form at that time, and much analysis remained to be done on that one study

alone, according to Dr. Peck's explanation quoted in the margin.[34]

Dr. Calderari recalled that the unblinded preliminary data on PALO-99-03 were sent to Helsinn [by the CRO conducting the study] in January, 2002, and that preliminary data "show efficacy for the product." (Dkt. 322 at 61.) He said that was a happy day at the company; "we were start seeing that our effort were paying off, but, of course, we were very careful because they were preliminary data." (Id.)

Helsinn sent a letter to CDER dated February 7, 2002 (the week after the critical date of January 30, 2002), stating in part as follows:

> In accordance with 21 CFR 312.47(b)(2), a pre-NDA meeting is requested in preparation for the palonosetron NDA. All phase 3 efficacy trials . . . have completed enrollment and preliminary efficacy data are available.

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[34] Dr. Peck described the process of analysis that spanned the period from the "unblinding" date to completion of the final study report as follows:

> The moment of unblinding, the data sets are now available for analysis. There's a mountain of data in this clinical trial. 600 -- or 500 and some patients, each patient observed for various values of one sort or another, including vomiting, probably 2 to 300 times. If you count the data items themselves, it's humongous. You don't just push a button and, bingo, there's your full study report ready to go to FDA. It's a very tedious effort. And even along the way, if they have not confirmed that certain assumptions were made with respect to the statistical analyses, they may go back to FDA and talk about . . . an alternative analysis.

(Dkt. 337 at 73–74.)

> Consistent with your letter of October 10, 2001, please find attached at Appendix #1 preliminary efficacy data for PALO-99-03. In this study, the preliminary data for Complete Response, which is the primary efficacy outcome measure for acute CINV, was 81.0% (153/189) for palonosetron 0. 25 mg, 73.5% (139/189) for palonosetron 0.75 mg, and 68.6%(127/185) for ondansetron 32 mg. Preliminary efficacy results for PALO-99-04 will be included in the background information package projected to be submitted four weeks prior to the meeting, and preliminary efficacy data for PALO-99-05 will be presented at the meeting.
>
> The following product information is provided to you regarding the suggested meeting:
>
> **Product name and application number**: Palonosetron HCl Intravenous Injection, 0.25 mg (0.05 mg/mL), or 0.75 mg (0.15 mg/mL). Please note that one of these product strengths will be selected for marketing approval based on the phase 3 efficacy data. The NDA number is 21-372.

(DTX-0264-0001.)

The tables of "preliminary efficacy data" attached to that Helsinn letter to the FDA dated February 7, 2002 letter were dated January 7, 2002. (Id. at -0009 to -0011.) Dr. Calderari testified that he could not recall when he first saw the data in those tables, but he would assume that he did see the data before January 15, 2002. (Dkt. 322

at 72.) Portions of two of those charts are shown in the margin.[35] See n. 37 infra and accompanying text.

[35] The tables attached to the February 7, 2002 Helsinn letter to the FDA, described as PALO-99-03 preliminary data, included the following content:

PALO-99-03

TABLE

Summary of Complete Response (Proportions) (n/%)
(Intent-to-treat Cohort)

	Treatment Group		
	Palonosetron 0.25 mg (N=80)	Palonosetron 0.75 mg (N=109)	Ondansetron 32 mg (N=183)
Period			
0 - 24 h	153 (81.0%)	199 (73.3%)	127 (68.8%)
>24 - 48 h	154 (81.5%)	132 (69.8%)	122 (65.8%)
>48 - 72 h	181 (83.2%)	147 (77.8%)	124 (67.0%)
>72 - 96 h	168 (88.9%)	151 (85.2%)	146 (79.4%)
>96 -120 h	175 (92.6%)	169 (89.4%)	151 (87.0%)
>24 120 h	140 (74.1%)	122 (64.6%)	102 (55.1%)
0 - 48 h	141 (74.6%)	110 (83.0%)	111 (60.0%)
0 - 72 h	137 (72.5%)	110 (81.4%)	97 (52.4%)
0 - 96 h	132 (69.8%)	112 (69.3%)	84 (50.0%)
0 -120 h	131 (69.3%)	111 (68.7%)	83 (50.3%)

N = Number of patients in specific group
n = Number of patients
Calculations of percentages based on N

(DTX-0264-0009.)

A further explanation of portions of the PALO-99-03 documents was provided at trial by Teva expert witness Dr. John Fruehauf. He is an M.D. clinical oncologist who also has a Ph.D. in pharmacology. He is a professor of clinical medicine and director of clinical pharmacology and developmental therapeutics at University of California Irvine. He has an active practice at the Chao Family Comprehensive Cancer Center, one of 43 comprehensive cancer centers in the United States. As director of developmental therapeutics, he is regularly involved in conducting Phase I, Phase II, and Phase III clinical trials. (Dkt. 324 at 5–8.)

Dr. Fruehauf and Dr. Peck testified as to their conflicting opinions on whether a person of ordinary skill in the clinical sciences would know, as of January 30, 2002, that palonosetron administered to a human reduces the likelihood of CINV, and specifically whether such person would know at that time that the 0.25 mg dosage claimed in the '219 patent was effective for CINV. (See generally dkt. 324 (Dr. Fruehauf); dkt. 337 (Dr. Peck).) That opinion testimony is discussed in Section II.A.4.b.2.

PALO-99-03

Summary of Complete Response (Confidence Intervals for Group Differences)
Intent-to-Treat Cohort)

	Difference		
	Palonosetron 0.25 mg - Ondansetron 32 mg (97.5% CI)	Palonosetron 0.75 mg - Ondansetron 32 mg (97.5% CI)	Palonosetron 0.75 mg - Palonosetron 0.25 mg (95% CI)
Period			
0 - 24 h	(1.8%, 22.8%)	(-8.1%, 16.9%)	(-16.4%, 1.0%)
>24 - 48 h	(4.8%, 28.1%)	(-7.4%, 15.2%)	(-20.7%, -2.6%)
>48 - 72 h	(2.0%, 22.4%)	(-8.1%, 21.4%)	(-16.7%, 0.0%)
>72 - 96 h	(1.8%, 19.0%)	(-8.8%, 18.3%)	(-11.6%, 4.3%)
>96 - 120 h	(-0.3%, 15.1%)	(-9.8%, 19.4%)	(-9.8%, 8.1%)
>24 - 120 h	(7.9%, 30.3%)	(-2.4%, 21.3%)	(-19.3%, 0.3%)
0 - 48 h	(5.3%, 33.9%)	(-8.8%, 14.8%)	(-21.8%, -1.0%)
0 - 72 h	(6.3%, 31.0%)	(-8.0%, 20.8%)	(-21.1%, -1.3%)
0 - 96 h	(7.1%, 30.7%)	(-2.8%, 20.2%)	(-20.1%, -1.0%)
0 -120 h	(7.4%, 30.7%)	(-2.8%, 20.8%)	(-20.7%, -1.4%)

(DTX-0264-0011.)

Testifying about the PALO-99-03 study documents themselves, Dr. Fruehauf stated that it was not surprising to see that the database was "unblinded" on January 2, 2002, and the three summary tables attached to Helsinn's February 7, 2002 letter to the FDA were dated January 7, 2002, less than a week after the data was unblinded. He pointed out that those tables, which do include some statistical analysis, are indicated at the bottom of each page to have been prepared using SAS. (Dkt. 324 at 61–63.)

Dr. Fruehauf explained that SAS is a widely accepted statistical package that was included in the pre-planned protocol for that Phase III study, "so before anybody went on this study, it was determined that this is what they would do." (Id. at 61.) On the other hand, referring to the later PALO-99-04 locked data, he did acknowledge that before the final reports of these Phase III studies were completed, "there were other things, statistics and other things that might be done" to analyze the locked data of those studies. (Id. at 204.)

Dr. Calderari, as head of the Helsinn palonosetron development program but not himself a clinician, was asked whether, upon receipt of that data in early 2002, he formed any conclusion as to whether palonosetron would definitely work for the reduction of CINV. He said no; "that was an indication that the first preliminary data set was positive; but...we, as part of the overall plan, we have to have two pivotal trials to be completed successfully in order to show efficacy of the product, so 99-03 and 99-04." (Dkt. 322 at 137–38.) When asked whether this data gave him confidence that both of those trials would successfully show efficacy, he replied, "[n]o, because unfortunately, as we know very well, drug development, . . . one trial is in-

dependent from the other one. You are also using different investigator, different countries, different populations, so there might be difference between two trials." (Id. at 138.)

Helsinn, together with its U.S. licensee and selected marketing partner MGI Pharma, issued a press release on January 16, 2002. The text of that announcement is quoted in full in the margin.[36]

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[36] The January 16, 2002 press release stated:

HELSINN HEALTHCARE SA, a privately owned Swiss pharmaceutical group, and MGI PHARMA, INC., (Nasdaq: MOGN) an oncology-focused pharmaceutical company based in Minneapolis, today announced that patient treatment is completed and the data analysis is underway for the pivotal Phase 3 trials of their investigational agent, Palonosetron. **Palonosetron** is a potent, highly selective 5-HT3-receptor antagonist in development in North America and Europe for the prevention of chemotherapy-induced nausea and vomiting (CINV). Submission of the New Drug Application (NDA) for Palonosetron is now planned to occur in the third quarter of 2002.

The Phase 3 clinical trial program was initiated in April 2000 and was designed to compare intravenous (IV) Palonosetron to currently marketed 5-HT3 antagonists. The trials were conducted at more than 130 medical centers across North America and Europe, with more than 1,800 cancer patients receiving either highly-or moderately-emetogenic chemotherapy. Based on the extended half-life of Palonosetron and the results of a Phase 2 trial, the efficacy of Palonosetron in the Phase 3 trial is being assessed over Day 2 though Day 5 following treatment, in addition to the primary efficacy measure of complete response during the 24-hour period after the start of chemotherapy.

"**We are pleased to have completed all patient treatment and to have begun analysis of the data collected in the Palonosetron Phase 3 clinical program,**" said Luigi Baroni, senior director of Scientific Affairs Division at HELSINN. "**The Phase 2**

11. Status as of patent application date, January 30, 2003

This section describes the chronology of the further palonosetron drug development events between the critical date of January 30, 2002, and the January 30, 2003 provisional application date of all four patents-in-suit.

It will be recalled that each of the three full-scale Phase III studies had reached the "last patient out" date in the fourth quarter of 2001. The clinical data from the earliest-completed study, PALO-99-03, had been "locked" on December 19, 2001, and had been "unblinded" and therefore available to be viewed by Helsinn on January 2, 2002. See Section I.C.10. The database of PALO-99-04 was locked on February 22, 2002 and that data was unblinded on February 28, 2002. (DTX-0289-0054.) The "locked" date for PALO-99-05 was March 14, 2002, and

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> **clinical trial results were promising, and we are hopeful that the Phase 3 Palonosetron data will demonstrate that it can make a difference for cancer patients suffering from CINV."** "**The half-life of other available 5-HT3 receptor antagonists ranges from approximately five to nine hours, where Palonosetron has a plasma elimination half-life of nearly 40 hours,**", notes Dr. John MacDonald, senior vice president of Research and Development at MGI. "**The activity seen with Palonosetron in the Phase 2 trial, coupled with its safety profile observed to date, led to the initiation of a Phase 3 program to assess the ability of the drug to provide prolonged protection against CINV with a single dose.**"
>
> (DTX-0040-0001 (emphasis in original).)

that data was unblinded on March 19, 2002. (DTX-0290-0023.)

The letter from Helsinn to the FDA, although dated and sent on February 7, 2002, has been described above as falling within the January 30, 2002 critical date period, because the tables of PALO-99-03 preliminary data attached to that letter were prepared and known to Helsinn before January 30, 2002. See Section I.C.10. Presumably that requested meeting with the FDA to review preliminary results of PALO-99-03, as well as preliminary results of PALO-99-04 and PALO-99-05 when available, did take place at a date not specified in the evidence.

The final reports on those three studies were named Clinical Study Reports. Those Reports for PALO-99-03 and for PALO-00-04 were each dated July 19, 2002. (DTX-288-0003; DTX-0289-0002.) The Clinical Study Report for PALO-00-05 was dated August 2, 2002. (DTX-0290-0002.) The Analysis Report of the re-analysis of Phase II study 2330 data, entitled "Fixed Dose Conversion and Historical Placebo Control Post-Hoc Efficacy Analysis (code PALO-00-01)," was dated August 8, 2002. (PTX-182.0003.)

The Clinical Study Report for PALO-99-03 was 250 pages long, exclusive of appendices. That report, with appendices, occupied 17 volumes in the subsequent NDA filing. (See DTX-0288-0003 and -0013 to -0018.) The Clinical Study Reports and appendices for PALO-99-04 and PALO-99-05 were comparable documents. (See DTX-0289 and DTX-0290.)

The Conclusion in the Synopsis section of the PALO-99-03 Clinical Study Report stated:

> In this study, non-inferiority of the 2 doses of palonosetron (0.25 mg and 0.75 mg) to ondansetron 32 mg was demonstrated for the complete response rate during the first 24 hours after chemotherapy, the primary efficacy parameter. Furthermore, non-inferiority of both palonosetron groups compared to ondansetron was also shown for most secondary efficacy parameters and palonosetron 0.25 mg was shown to be superior to ondansetron with regard to most of these secondary efficacy parameters. Thus, palonosetron 0.25 mg showed a better efficacy profile over ondansetron during the delayed phase of nausea and vomiting. The rate of patients with adverse events was comparable in the treatment groups and showed a similar pattern. There were no safety concerns associated with results of laboratory parameters, vital signs and ECG recordings and Holter monitoring measured during the study.

(DTX-0288-0012.) The corresponding Conclusion sections of the PALO-99-04 and PALO-99-05 Clinical Study Reports contained similar types of information. (See DTX-289-0012; DTX-0290-0011.)

The Synopsis section of the PALO-99-03 Clinical Study Report also contained exactly the same efficacy summary numbers that had been communicated to the FDA in the preliminary data tables attached to Helsinn's letter dated February 7, 2002. See n. 35 supra. Those numbers were set forth in Table 1 and Table 2 of the Syn-

opsis, as also contained in the appendix materials submitted with that Report. (See DTX-0288-0009 and -0095.) Those two tables are shown in the margin.[37]

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[37] The tables shown under "Efficacy results" in the Summary portion of the Synopsis section of the PALO-99-03 Clinical Study Report were as follows:

Synopsis continued

Name of Sponsor/Company: Helsinn Healthcare SA	Individual Study Table Referring to Part of the Dossier	(For National Authority Use only)
Name of Finished Product:	Volume:	
Name of Active Ingredient: Palonosetron HCl	Page:	

Statistical methods (continued): Differences between the treatment groups regarding time to first emesis episode, time to first administration of rescue medication and time to treatment failure were analysed using Kaplan-Meier estimates and a Log-Rank test.
Incidences for adverse events were calculated overall, by category, by body system and by preferred term. In addition, 95% CI were provided for the overall incidence and for the incidence by category of adverse events in each treatment group. Changes in laboratory values with respect to toxicity grades were investigated for each time point within each group using Wilcoxon matched pairs signed rank test. All other safety parameters were analyzed descriptively.

Summary
Efficacy results:
The proportion of patients who achieved a complete response and the results from the statistical analysis of the primary efficacy parameter complete response rate during the first 24 hours after chemotherapy are displayed in Table 1, whereas in Table 2 the 97.5% CIs of the difference in CR rate of each dose of palonosetron versus ondansetron are depicted.

Table 1: Patients with a complete response rates during the first 24 hours after chemotherapy (ITT cohort, N = 563)

Time period [hours]	Palonosetron 0.25 mg (N = 189)		Palonosetron 0.75 mg (N = 188)		Ondansetron 32 mg (N = 185)	
	N	%	N	%	N	%
0-24	153	81.0	139	73.5	127	68.6

Table 2: The 97.5% confidence interval for the difference in complete response rates during the first 24 hours after chemotherapy between the palonosetron groups and the ondansetron group (ITT cohort, N = 563)

	Palonosetron 0.25 mg minus ondansetron 32 mg	Palonosetron 0.75 mg minus ondansetron 32 mg
97.5% CI	[1.8%; 22.8%]	[-6.1%; 15.9%]

The lower limit of the 97.5% confidence interval for the difference in complete response rates during the first 24 hours after chemotherapy was above -15% (pre-set threshold) for both comparisons of palonosetron to ondansetron 32 mg. Therefore, the non-inferiority of both palonosetron doses to ondansetron 32 mg was demonstrated for the prevention of moderately emetogenic chemotherapy-induced nausea and vomiting. Furthermore, the lower limit of the 97.5% confidence interval of the comparison palonosetron 0.25 mg with ondansetron was above zero, indicating superior complete response rates in the palonosetron 0.25 mg group compared to the ondansetron group. The results from the PP cohort were consistent with the ITT analysis.

(DTX-0288-0009.)

The detailed contents of the PALO-99-03 Clinical Study Report, following the Synopsis, included a narrative headed Additional changes after unblinding. Portions of that section are also quoted in the margin.[38]

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[38] That portion of the PALO-99-03 Clinical Study Report stated in part as follows:

> • Additional statistical analyses.
>
> An additional statistical analysis was performed for the number of emetic episodes, which presented the number of patients with 0, 1, 2 and ≥ 3 emetic episodes for each time interval. Furthermore, quartiles were calculated for quality of life, time to first emetic episode, time to treatment failure, time to the first administration of rescue medication and patients global satisfaction because median, mean, minimum and maximum values did not show the differences between the treatment groups, which were seen by statistical testing. Further additional analyses were performed on dosage and time of infusion of chemotherapy given on Day 1.
>
> . . . .
>
> • Change in the statistical analysis.
>
> The normal distribution of data (number of emetic episodes, patient global satisfaction, quality of life) was to be assessed by the Shapiro-Wilk test before the application of parametric tests. However, the non-normality was obvious form [sic: from] the summary tables. Therefore, the Shapiro-Wilk test was omitted and a non-parametric method was used.
>
> . . . .
>
> • Trial validation.
>
> A new formula for the trial validation was developed because a mistake was detected in the database. Moreover, additional information regarding the percentage of patients in each study treatment arm using concomitant steroids was added. It was decided to consider both formulas (original and updated formulas) for the validation of study PALO-99-03.

(DTX-0288-0071, -0072 (bracketed text added).)

Helsinn filed its New Drug Application, NDA 21-372, on September 27, 2002, approximately one month after the above-listed clinical reports were completed. (See PTX-121.) All of those reports, as well as voluminous other data, were included in that NDA filing. (See NDA number 21-372 on each title page of above-cited report exhibits.) Helsinn sent additional submissions to the FDA dated October 11 and November 21, 2002, January 24, April 9, April 24, May 15, June 9, June 13, June 18, June 20, June 25, July 1, July 17, and July 22, 2003. (See PTX-121.)

Helsinn made at least one publication of some of its unblinded Phase III data during the period between January 30, 2002 and the patent application date of January 30, 2003. That was an oral presentation accompanied by an abstract, authored by Helsinn's Dr. Macciocchi and research colleagues Steven M. Grunberg et al., described as "for the PALO-99-04 Study Group." ("the Grunberg abstract"). It was entitled "Palonosetron is active in preventing acute and delayed emesis following moderately emetogenic chemotherapy: Results of a phase III trial." (PTX-297.0002.)

The Grunberg abstract was presented at the June 23-26, 2002 conference of the Multinational Association of Supportive Care in Cancer in Boston. (PTX-297.0001.) At that time, the PALO-99-04 data had been unblinded and under analysis since February 28, 2002, and the final Clinical Study Report would be completed and dated July 19, 2002. Also, of course, the data of the companion study, PALO-99-03, had been unblinded and under analysis since January 2, 2002, and its Clinical Study Report would also be dated July 19, 2002. See Section I.C.11.

There was text and a table in the one-page Grunberg abstract. The table showed efficacy results of Helsinn's 0.25 mg. and 0.75 mg palonosetron dose levels in comparison with dolasetron, for acute and delayed CINV in moderately emetogenic chemotherapy, as the PALO-99-04 trials had studied. The Conclusion stated in the Grunberg abstract was: "Palonosetron has demonstrated significant activity in preventing both acute and delayed emesis with a single I.V. dose in patients receiving moderately emetogenic chemotherapy. Palonosetron was safe and well tolerated." (PTX-297.0002.)

Helsinn filed Provisional Patent Application No. 60/444,351 at the U.S. Patent and Trademark Office on January 30, 2003. (See dkt. 289 (patent family history chart).) On that date, Helsinn's New Drug Application 21-372 was still pending at the FDA.[39]

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[39] FDA approval of Helsinn's NDA 21-372 was issued on July 25, 2003. The approval letter stated in pertinent part:

> This new drug application provides for the use of Aloxi® (palonosetron hydrochloride injection) for:
>
> 1) the prevention of acute nausea and vomiting associated with initial and repeat courses of moderately and highly emetogenic cancer chemotherapy, and
>
> 2) the prevention of delayed nausea and vomiting associated with initial and repeat courses of moderate emetogenic cancer chemotherapy.
>
> We completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

(PTX-121.0001, -.0015.)

12. Issuance of patents-in-suit

The procedural history of the prosecution of the patents-in-suit, subsequent to the filing date of the provisional application on January 30, 2003, has been summarized in this Court's claim construction Memorandum Opinion filed in this case on April 22, 2015. (See dkt. 290 at 16–18.) Here we briefly summarize the basic chronology of those prosecution events, omitting record citations that are stated in that earlier Opinion.

The first generation of patents to be issued subsequent to the January 30, 2003 provisional application date were the '724 and '725 patents-in-suit, dated May 24, 2011. Thus, the original prosecution for this patent family took approximately 8½ years. The next patent-in suit, the '424 patent, was issued on June 14, 2011.

The '724, '725, and '424 patents, all sharing a contemporaneous prosecution era, were approved only after appeals in all three cases to the Commissioner of Patents. Much file history was accumulated in those prosecution files.

The '219 patent, with the same provisional application date and an actual filed application date of May 23, 2013, was issued on December 3, 2013. That patent was applied for and granted during the pendency of this litigation. The application history of the '219 patent itself, albeit not as extensive as for the other three patents, includes many of the materials filed in this litigation including expert reports. (See '219 patent, pages 1–6.) The other patents issued to date in this patent family tree, and abandoned applications, are listed in the chart supplied by the parties. (Dkt. 289.)

13. Claim construction rulings regarding prosecution history

This Court has issued claim construction opinions interpreting some claim limitations of the patents-in-suit pertaining to both the stability and the efficacy aspects of the claims. Those opinions were filed during claim construction proceedings in this case and in a related case, Civil Action No. 12-2867.

The claim construction Memorandum Opinion filed in this case, on April 22, 2015, addressed the issue of whether the following portion of the preamble of claim 1 of the '219 patent constitutes claim limitation language: "for intravenous administration to a human to reduce the likelihood of cancer chemotherapy-induced nausea and vomiting." This Court ruled that language to be limiting in its entirety. (Dkt. 290.) The discussion in that opinion included a review of portions of the prosecution history of all of the patents-in-suit, as it was recognized that the earlier patent histories can be relevant to interpreting the claims of later-issued patents in the same family.

That opinion described, inter alia, a phase early in the prosecution of the '724, '725, and '424 patents when the examiners rejected the term "preventing emesis" in applied-for preambles to each of those patents under 35 U.S.C. § 112 (enablement). (See dkt. 290 at 20.) The applicants overcame that ground for rejection in each of those applications by substituting the words "for reducing emesis or reducing the likelihood of emesis." (Id.)

To overcome that ground for rejection, the applicants successfully argued as follows, in a telephone interview with the examiners quoted from here in the file history of the '424 patent:

> During the telephone interview, a proposed amendment to the claims in the '270 application was discussed. Applicant understood the Examiner's primary concern with the claims to be with the word "preventing," recited in independent claims 1 and 11 of the '270 application. Applicant indicated that palonosetron has been approved by the Food and Drug Administration for preventing emesis, and is marketed as a drug for preventing emesis.
>
> The Examiners suggested that an amendment to independent Claims 1 and 11 in the '270 application, wherein Applicant includes the phrase "reducing the likelihood" of emesis instead of "preventing" emesis, would address the Office's concerns. Applicant has amended the claims in this application in accordance with the Examiners' suggestions for the '270 application.

(Dkt. 178-3 at 116 (Examiners' Summary of July 27, 2006 Telephonic Interview).)

This portion of the common prosecution history of the patents-in-suit may be relevant to the on-sale bar issues in this case, discussed in Section II.A.4.

14. ANDA filings by Teva and others

Teva's Abbreviated New Drug Application ("ANDA") seeks approval for a generic Aloxi® product that can have one of two dosage strengths: (1) a 0.25 mg/5 ml dosage strength, used to prevent chemotherapy-induced nausea and vomiting ("the CINV dosage strength"); and (2) a

0.075 mg/1.5 ml dosage strength, used to prevent postoperative nausea and vomiting ("the PONV dosage strength"). (See dkt. 207 at 4.) The concentration of both proposed Teva products is 0.05 mg/mL, because the 0.25 mg dose solution is 5 ml and the 0.075 mg dose solution is 1.5 ml.

II. CONCLUSIONS OF LAW[40]

A. On-sale bar

The Court will now turn to the issue of the on-sale bar and its application to this case. "[T]he patent system represents a carefully crafted bargain that encourages both the creation and the public disclosure of new and useful advances in technology, in return for an exclusive monopoly for a limited period of time." Pfaff v. Wells Elec., Inc., 525 U.S. 55 (1998). Before 2011, Section 102 of the Patent Act balanced this "carefully crafted bargain" by providing that:

> A person shall be entitled to a patent unless(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of the application for patent in the United States . . . .

35 U.S.C. § 102, amended by Leahy-Smith America Invents Act, Pub.L. No. 112-29, 125 Stat. 254 (2011) (emphasis added) ("AIA"). This provision, referred to as the

[40] To the extent that the "Conclusions of Law" portion of this opinion contains findings of fact in addition to those expressly set out under the heading "Findings of Fact," they shall be deemed to be part of the findings of fact.

on-sale bar, serves as a bar to patentability if the claimed invention is (1) made the "subject of a commercial offer for sale," and (2) the invention is "ready for patenting." See Pfaff, 525 U.S. at 67. A sale under this bar occurs when the parties offer or agree to reach a contract "to give and pass rights of property for consideration which the buyer pays or promises to pay the seller for the thing bought or sold." Zacharin v. United States, 213 F.3d 1366, 1370 (Fed. Cir. 2000) (quotation and citation omitted).

1. Legal standards and post-AIA statutory construction

a. Historical analysis

Historically, a secret sale or offer for sale of a claimed invention has precluded patentability under the on-sale bar. See Metallizing Eng'g Co. v. Kenyon Bearing & Auto Parts Co., 153 F.2d 516 (2d Cir. 1946) (Hand, J.) ("[I]t is a condition upon an inventor's right to a patent that he shall not exploit his discovery competitively after it is ready for patenting; he must content himself with either secrecy, or legal monopoly."); Egbert v. Lippman, 104 U.S. 333 (1881). The invention at issue in *Egbert*, a corset improvement, was given by the inventor to a woman who wore the corset under her dress, rendering it unobservable to the general public. See Egbert, 104 U.S. at 337. The Supreme Court found that the inventor's corset improvement was in public use, noting that "[i]f an inventor, having made his device, gives or sells it to another . . . without limitation or restriction, or injunction of secrecy, and it is so used,

such use is public, even though the use and knowledge of the use may be confined to one person." See id.[41]

The legal principle set forth in Egbert—that a claimed invention given or sold to one individual or entity in secrecy can constitute a public use—has proliferated a line of precedent in which secret sales or offers for sale bar patentability. See, e.g., Special Devices, Inc. v. OEA, Inc., 270 F.3d 1353, 1357–58 (Fed. Cir. 2001) (finding that on-sale bar invalidated patent, although contract for sales of invention was only for purpose of commercial stockpiling by supplier and sales were confidential); Woodland Trust v. Flowertree Nursery, Inc., 148 F.3d 1368, 1370 (Fed. Cir. 1998) ("Thus an inventor's own prior commercial use, albeit kept secret, may constitute a public use or sale under § 102(b), barring him from obtaining a patent."); Hall

[41] The Court notes that pre-AIA § 102 language also included a public use bar. See 35 U.S.C. § 102, amended by § 102(a)(1), 125 Stat. at 285-86 ("A person shall be entitled to a patent unless . . . (b) the invention was . . . in public use . . . ."). As a historical note, the public use and on-sale bars were often not differentiated by courts, or were referred to using other terminology. See, e.g., Metallizing Eng'g Co., 153 F.2d at 520 (borrowing statutory language from Patent Act of 1839 and referring to on-sale and public use bars as "prior use"). The relationship between the § 102 bars was explained by the Supreme Court in Pfaff:

> We originally held that an inventor loses his right to a patent if he puts his invention into public use before filing a patent application. His voluntary act or acquiescence in the public sale and use is an abandonment of his right. A similar reluctance to allow an inventor to remove existing knowledge from public use undergirds the on-sale bar.

Pfaff, 525 U.S. at 64 (quoting Pennock v. Dialogue, 27 U.S. 1 (1829) (Story, J.)).

v. Macneale, 107 U.S. 90, 96 (1883) (finding that an inventor's "burglar-proof" safes were in public use after inventor sold three safes, despite testimony that technology was completely concealed within safe).

On September 16, 2011, the AIA was signed into law with the objective of "establish[ing] a more efficient and streamlined patent system that will improve patent quality and limit unnecessary and counterproductive litigation costs." (Dkt. 236-3 at 81 (AIA Committee Report).) The AIA's most significant change was the conversion of the United States' patent system from a "first-to-invent" to a "first-inventor-to-file" system, which now "encourages the prompt filing of patent applications" and redefines the effective filing date as the date of the patent application, rather than the date of the invention. See 35 U.S.C. § 100(i)(1)(A) (1-24-2008 Committee Report).[42]

In converting to a first-inventor-to-file system, Congress attempted to modernize and streamline many facets of the patent system, including the identification of prior art. (See dkt. 236-3 at 83–84 (AIA Committee Report) ("Prior art will be measured from the filing date of the application and will typically include all art that publicly exists prior to the filing date, other than disclosures by the inventor within 1 year of filing.").) As discussed above, the on-sale bar analysis under the Egbert rationale had led to unusual or extreme results for patentees who sought to obtain a patent after such secret use or sales. (See id. at 17 (statement of Senator Kyl in Mar. 8, 2011 Congressional Record, in which he describes effect of on-sale bar

[42] As will be discussed later, Plaintiffs argue that this overall change to the patent system also supports a new interpretation of the on-sale bar.

and public use bar as "impos[ing] extreme results to no real purpose.").)

The AIA thus redefined the scope of prior art under § 102 as follows:

> A person shall be entitled to a patent unless—(1) the claimed invention was patented, described in a printed publication, or in public use, on sale, or otherwise available to the public before the effective filing date of the claimed invention . . . .

35 U.S.C. § 102(a)(1).

The AIA added the clause "otherwise available to the public," and also regrouped the categories of prior art under § 102. Compare 35 U.S.C. § 102, amended by § 102(a)(1), 125 Stat. at 285–86 (designating prior art categories as follows: "patented or described in a printed publication in this or a foreign country or in public use or on sale in this country . . . ."), with 35 U.S.C. § 102(a)(1) (designating prior art categories as: "patented, described in a printed publication, or in public use, on sale, or otherwise available to the public. . . .").

b. Parties' arguments regarding on-sale bar

It is against this historical and statutory background that this Court decides whether § 102(a)(1) of the AIA requires a sale or offer for sale of a claimed invention to be "available to the public before the effective filing date" of the claimed invention in order for the on-sale bar to apply

and possibly invalidate a patent. (See generally dkt. 204; dkt. 209; dkt. 226; dkt. 236.)[43]

Plaintiffs argue, as a threshold matter, that the '219 patent is subject to the AIA. (See dkt. 209 at 18–19.) The AIA states in pertinent part:

> [T]he amendments made by this section shall take effect upon the expiration of the 18-month period beginning on the date of the enactment of this Act [September 16, 2011], and shall apply to any application for patent, and to any patent issuing thereon . . . .

35 U.S.C. § 3(n).

Plaintiffs additionally argue that the AIA established a new standard for the on-sale bar, i.e., that commercial sales or offers for sale of the invention must now be made available to the public for the on-sale bar to apply. (See dkt. 209 at 7.) Plaintiffs argue that the contracts with service providers Oread, Inc. ("Oread") and SP Pharmaceuticals L.L.C. ("SP"), and the licensing and supply agreements with MGI Pharma, Inc. ("MGI") were not commercial sales or offers for sale. (See id.) Plaintiffs argue in the alternative that even if this Court considers these contracts to be commercial sales or offers for sale, the post-

[43] Defendant, in its opposition to Plaintiffs' motion for partial summary judgment, relied in part on Sandoz's motion for summary judgment of invalidity of the '219 patent under the on-sale bar. (See dkt. 226 at 8, n. 1.) Sandoz's motion for summary judgment was terminated by way of a consent judgment but will be cited to in this Memorandum Opinion insofar as Defendant incorporated these arguments into this motion. (See dkt. 247.)

AIA on-sale bar applicable to the '219 patent does not apply because the contracts never made the invention available to the public. (See id.)

Teva argues that the AIA did not amend the on-sale bar to include a public sale requirement. (See dkt. 226 at 9.) Teva asserts that under the correct interpretation of the AIA, Helsinn violated the on-sale bar by executing a supply agreement for the marketing and sale of Aloxi with MGI. (See id. at 10.) Teva additionally argues that Helsinn violated the on-sale bar even under Helsinn's proposed interpretation of the AIA, as the supply agreement was publicized and MGI is a member of the public. (See id.)

c. Interpreting the legal standard

1. Statutory construction

The Court's first inquiry in interpreting a statute "is to determine whether the language at issue has a plain and unambiguous meaning with regard to the particular dispute in the case. Our inquiry must cease if the statutory language is unambiguous and the statutory scheme is coherent and consistent." Bettcher Indus., Inc. v. Bunzi, USA, Inc., 661 F.3d 629, 644 (Fed. Cir. 2011) (quotation and citation omitted).

The parties in this case dispute whether the last clause of § 102(a)(1), "otherwise available to the public," modifies the section's previous clauses or serves as its own category of prior art. (See dkt. 209 at 21 ("Since the modifier 'or otherwise available to the public' in § 102(a)(1) is a catchall phrase, it applies to each preceding category of prior art in that section that must make the claimed invention available to the public, including an alleged 'sale.'"); but see dkt. 226 at 20 ("[T]he phrase 'or otherwise

available to the public' creates a residual category of prior art to capture invalidating disclosures that do not fall into one of the enumerated categories in section 102.").)

This Court is guided by the Supreme Court's "common sense" approach to statutory interpretation. See Paroline v. United States, 134 S. Ct. 1710 (2014) ("Reading the statute to impose a general proximate-cause limitation accords with common sense.").[44] The statute at issue in Paroline included six categories of covered losses and a final clause that covered "any other losses suffered by the victim as a proximate result of the offense." See id. at 1720. The victim argued that the proximate causation requirement only applied to the final "catchall" category in the statute. See id. at 1720–21. The Court disagreed, holding that "[w]hen several words are followed by a clause which is applicable as much to the first and other words as to the last, the natural construction of the language demands that the clause be read as applicable to all." Id. at 1721 (quotation and citation omitted).

The Paroline court further noted that "[i]t is . . . a familiar canon of statutory construction that [catchall] clauses are to be read as bringing within a statute categories similar in type to those specifically enumerated." Id. This "familiar canon of statutory construction," the associated-words canon, arises when words "are associated in

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[44] The Supreme Court references the surplusage canon of statutory construction, which provides that "[i]f possible, every word and every provision is to be given effect . . . . None should be ignored. None should needlessly be given an interpretation that causes it to duplicate another provision or to have no consequence." ANTONIN SCALIA & BRYAN A. GARNER, READING LAW: THE INTERPRETATION OF LEGAL TEXTS 174 (1st ed. 2012). Justice Scalia noted that this truism applies to "all sensible writing." See id.

a context suggesting that the words have something in common." SCALIA & GARNER, supra note 44, at 195. These associated words often "involve listings," but a list is by no means a prerequisite. See id. at 197. When applying the associated-words canon, "[the words] should be assigned a permissible meaning that makes them similar." Id. at 195.

A court must begin with "the assumption that the ordinary meaning of the language chosen by Congress accurately expresses the legislative purpose." See Microsoft Corp. v. i4i Ltd. P'ship, 131 S. Ct. 2238 (2011) (internal quotation and citation omitted). The use of a term of art, or a "common-law term," generally carries with it the assumption that "the term . . . comes with a common law meaning, absent anything pointing another way." See id. In addition, "when Congress employs a term of art, it presumably knows and adopts the cluster of ideas that were attached to each borrowed word in the body of learning from which it is taken." Air Wisc. Airlines Corp. v. Hoeper, 134 S. Ct. 852, 861-62 (2014). This inquiry will require, as discussed below, a review of a statute's legislative history and the "body of learning" from which the words originated. See id. at 862.

2. Agency guidelines

In the context of patent law, guidelines published by the United States Patent and Trademark Office ("USPTO") are also instructive in interpreting a statute as they provide a practitioner's perspective on a given issue. See, e.g., Examination Guidelines for Implementing the First Inventor to File Provisions of the Leahy-Smith America Invents Act, 78 Fed. Reg. 11,059, 11,075 (Feb. 14, 2013) (to be codified at 37 C.F.R. 1). While the USPTO

guidelines typically serve as a "guide to patent attorneys and patent examiners on procedural matters," a court may take judicial notice of guidelines so long as the USPTO's interpretation does not conflict with the statute. See Molins PLC v. Textron, Inc., 48 F.3d 1172, 1180 n. 10 (Fed. Cir. 1995). It should be noted, however, that these guidelines are not binding on a court. See Enzo Biochem, Inc. v. Gen–Probe Inc., 323 F.3d 956, 964 (Fed. Cir. 2002).

3. Legislative history

This Court must give effect to congressional intent by "look [ing] not only to the particular statutory language, but to the design of the statute as a whole and to its object and policy." Crandon v. United States, 494 U.S. 152, 158 (1990) (citation omitted). Committee Reports, "which represent the considered and collective understanding" of Congress "in drafting and studying proposed legislation," are crucial when considering an issue of first impression. In re Swanson, 540 F.3d 1368, 1376 (Fed. Cir. 2008) (quotation and citation omitted). Although the Supreme Court has identified the Committee Report as the authoritative source on discerning legislative intent, House and Senate records are also instructive in determining a statute's underlying policy. See Bettcher Indus., 661 F.3d at 646 (using relevant House and Senate records to "confirm" interpretation of § 317 of Patent Act).

Prior versions of statutory provisions may also supply further evidence of congressional intent. See Russello v. United States, 464 U.S. 16, 23 (1983) In Russello, the Supreme Court interpreted a section of the RICO chapter of the Organized Crime Control Act of 1970 by applying the "ordinary meaning of the words used." See id. at 21 (quotation and citation omitted). The Court's interpretation

was bolstered by earlier proposed versions of the legislation, which contained a limiting definition of the word at issue. See id. at 23–24. The Court held that "[w]here Congress includes limiting language in an earlier version of a bill but deletes it prior to enactment, it may be presumed that the limitation was not intended." Id. This principle does not only apply to prior limiting language. When looking to prior versions of legislation, courts should "not assume that Congress intended to enact statutory language that it has earlier discarded in favor of other language." See Chickasaw Nation v. United States, 534 U.S. 84, 93 (2001) (internal quotation and citation omitted).

4. Public policy considerations

The last factor that this Court will consider in interpreting § 102(a)(1) is the public policy underlying the passage of the ALA in its entirety. "[T]he meaning of statutory language, plain or not, depends on context." Holloway v. United States, 526 U.S. 1 (1999). Thus, it is essential to consider the AIA's other amendments and Congress's policy goals in enacting them, as these changes illustrate the overarching statutory scheme. See Bettcher Indus., 661 F.3d at 644 ("It is a fundamental canon of statutory construction that the words of a statute must be read in their context and with a view to their place in the overall statutory scheme."). The importance of interpreting a statute in the context of the larger statutory scheme is crucial, as "Congress . . . does not alter the fundamental details of a regulatory scheme in vague terms or ancillary provisions—it does not, one might say, hide elephants in mouseholes." Whitman v. Am. Trucking Ass'ns, 531 U.S. 457 (2001).

d. Application of legal standards

The Court will now consider the parties' specific arguments regarding their proposed interpretation of § 102(a)(1) of the AIA.

1. Statutory construction

Plaintiffs assert that the plain language of § 102(a)(1) supports their interpretation that a patent may only be invalidated under the AIA's on-sale bar if the claimed invention was made available to the public prior to its effective filing date. (See dkt. 209 at 19.) They argue that the phrase "otherwise available to the public" is a modifying clause that is "applicable as much to the first and other words as to the last." (See id. at 21 (quotation omitted).)

The United States Court of Appeals for the Federal Circuit ("Federal Circuit"), Plaintiffs claim, has endorsed the same interpretation of modifying clauses. (See id.) In Resource Conservation Group, LLC v. United States, 597 F.3d 1238 (Fed. Cir. 2010), the Federal Circuit held that the theory of last antecedent—wherein qualifying words refer solely to the last antecedent—is "overcome by other factors showing a different meaning." See Res. Conservation Grp., *LLC*, 597 F.3d at 1245. In Finisar Corp. v. DirecTV Grp., Inc., 523 F.3d 1323 (Fed. Cir. 2008), the Federal Circuit held that "when a modifier is set off from a series of antecedents by a comma, the modifier should be read to apply to each of those antecedents." See Finisar Corp., 523 F.3d at 1336–37. Plaintiffs argue that the placement of the modifying clause "otherwise available to the public," bolstered by the Supreme Court and Federal Circuit interpretations of similar clauses, renders the statute's language unambiguous. (See dkt. 209 at 20.)

Defendant sets forth two statutory interpretation arguments in opposition to Plaintiffs: (1) the term "on sale" is a term of art that was left unchanged in the AIA and thus the prior meaning still applies; and (2) "otherwise available to the public" is a disjunctive phrase that is meant to serve as a residual category of publicly available prior art. (See dkt. 226 at 18–21.)

Defendant first argues that "when Congress employs a term of art, it presumably knows and adopts the cluster of ideas that were attached to each borrowed word in the body of learning from which it is taken." (See id. at 19 (quotation and citation omitted).) Teva provides the example of the phrase "a patent shall be presumed valid," which the Supreme Court held as requiring a clear and convincing evidence standard. (See id.) See also Microsoft Corp., 131 S. Ct. at 2246. The Supreme Court reasoned that the clear and convincing evidence standard applies "because courts before 1952 had interpreted the presumption in that manner." (See dkt. 226 at 19.) See also In re Nuijten, 500 F.3d 1346 (Fed. Cir. 2007) (concluding that by reenacting "manufacture" as a category of patentable subject matter in 1952, despite other changes to 35 U.S.C. § 101, Congress intended to adopt pre-1952 judicial definitions of the term "manufacture"). Defendant argues that Plaintiffs have not "overcome this presumption." (See dkt. 226 at 20; cf. dkt. 204 at 29 ("If Congress had intended to graft a new 'public' requirement onto the on-sale bar, it could have done so explicitly by adding a 'public' modifier to 'on sale' . . . just as section 102 contains the phrases 'printed publication' and 'public use.'").)

Teva also claims that "otherwise available to the public" constitutes a residual category "to capture invalidating disclosures that do not fall into one of the enumerated

categories in section 102." (See dkt. 226 at 20.) Defendant distinguishes Paroline and Resource Conservation by noting that "[n]othing in Paroline—or in Resource Conservation for that matter—suggests that the addition of a catch-all category to a pre-existing statute could change the established meaning of language retained in the statute." (See id. at 21 (emphasis in original).) Teva also highlights Plaintiffs' failure to cite to any case "where an amendment to include a residual 'or otherwise' clause had the effect of deleting decades of precedent. . . ." (Id.)

Plaintiffs flatly disagree with Defendant's argument that "Congress has left the . . . language [of § 102] virtually unchanged from the original 1836 Act." (See dkt. 226 at 19.) Plaintiffs first point out that "the language surrounding the words 'on sale' did change significantly under the AIA." (See dkt. 236 at 9.) Plaintiffs note that the elimination of geographic limitations, the regrouping of different prior art categories, and the addition of "otherwise available to the public" indicate that § 102(a) was not left "virtually unchanged." (See id.) Plaintiffs add that the Defendant's cases discussing an unchanged words presumption are distinguishable because Congress, in those cases, "amended the statutes to include terms of art." (See id. at 9 n. 3.) Here, Plaintiffs assert, Congress "changed the surrounding language in providing a new legal standard, which it elucidated in the legislative history." (Id. at 9.)

Plaintiffs also argue that the Defendant's argument for a residual category that "has no bearing on the scope of the separate 'on sale' category" requires that the word "otherwise" be interpreted as surplusage, which would violate the surplusage canon of statutory interpretation. (See id. at 8.) See also SCALIA & GARNER, supra note 44, at 174.

2. Agency guidelines

Plaintiffs bolster their statutory interpretation argument by referencing the USPTO's published guidelines on § 102(a). (See dkt. 209 at 20.) Plaintiffs note that the USPTO published guidelines after a comment period and its own statutory interpretation analysis, and concluded that "secret sale or use activity does not qualify as prior art." (See id.) The guidelines define a sale or offer for sale as secret "if, for example, it is among individuals having an obligation of confidentiality to the inventor." (Id. at n. 10 (quotation and citation omitted).) Plaintiffs note that the USPTO instructed that the "relevant inquiry is focused on 'whether the sale . . . made the invention available to the public.'" (Id.)

Teva emphasizes that the USPTO guidelines are nonbinding on this Court. (See dkt. 226 at 33.) See also Enzo Biochem, Inc., 323 F.3d at 964. Defendant notes that the USPTO acknowledges that the guidelines were issued "as a practical matter" until "the courts . . . ultimately address questions concerning the meaning of AIA 35 U.S.C. § 102." (Id. (quotation and citation omitted).) Defendant argues that because the USPTO intended these guidelines only to serve as temporary guidance, the Court need not consider them. (See id.)

Plaintiffs reply that it is significant that the USPTO arrived at the same interpretation of § 102(a)(1) as the Plaintiffs "after a comprehensive study, which included a thorough analysis of the legislative history." (See dkt. 236 at 14.) Plaintiffs note that the USPTO's interpretation of the AIA should not be "downplay[ed]." (See id.)

3. Legislative history

Plaintiffs argue that the legislative history confirms their plain meaning interpretation of § 102(a)(1). (See dkt. 209 at 22.) They note that the Committee Report is "the most persuasive [source] . . . on the bill in question" because it incorporates by reference the Senate hearings in which the AIA's sponsor, Senator Kyl, explained the AIA's on-sale bar. (See id. at 22-24.) Plaintiffs claim that Senator Kyl's statements in these hearings highlight the congressional intent to require that a claimed invention be made available to the public in order for the on-sale bar to apply. (See id. at 23.) Plaintiffs cite the record from the March 8, 2011 Senate hearing in pertinent part: "The word 'otherwise' makes clear that the preceding clauses describe things that are of the same quality or nature as the final clause—that is, although different categories of prior art are listed, all of them are limited to that which makes the invention 'available to the public.'" (Dkt. 236-3 at 16 (Mar. 8, 2011 Congressional Record).) In a September 8, 2011 hearing on the final bill, Senator Kyl stated:

> As Chairman Smith most recently explained in his June 22 remarks, "contrary to current precedent, in order to trigger the bar in new 102(a) in our legislation, an action must make the patented subject matter 'available to the public' before the effective filing date." . . . When the committee included the words "or otherwise available to the public" in section 102(a), the word "otherwise" made clear that the preceding items are things that are of the same quality or nature. As a result, the preceding events and things are limited to those that make the invention "available to the public."

(Id. at 237 (Sept. 8, 2011 Congressional Record).)

Defendant sets forth two arguments in opposition to the Plaintiffs: (1) the AIA is a culmination of Congress's prior attempts to enact patent reform in 2005, 2007, 2008, and 2009—all of which left the on-sale bar unchanged; and (2) Plaintiffs' interpretation of the AIA's legislative history improperly relies on a "minority view." (See dkt. 226 at 22–31.)

Teva notes that attempts were made in 2005 and 2008 to "expressly change [ ] the on-sale bar to exclude non-public sales, and did not pass." (Id. at 23.)[45] Other attempts at patent reform, particularly in 2007 and 2009, retained the "public use" and "on sale" categories of prior art. (See generally id. at 23–27.)[46] Defendant argues that the House's 2007 patent reform bill maintained the on-sale bar because of "how the terms 'in public use' and 'on sale' have been interpreted by the courts" and because "there is nothing inherent in a first-to-file system that will deter inventors from making use of their inventions as trade secrets and then some time later filing a patent application for the invention." (See id. at 24 (citation omitted).) Teva notes that despite the inclusion of the phrase "otherwise available to the public" in the 2007 and 2009 bills, Senator Kyl objected to the 2009 Senate bill because

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[45] The wording of this rejected amendment defined invalidating prior art as that which is "patented, described in a printed publication, or otherwise publically [sic] known." (See dkt. 226 at 23.) The 2008 proposed amendment defined invalidating prior art as that which is "patented, described in a printed publication, or otherwise made available to the public (other than through testing undertaken to reduce the invention to practice)." (See id. at 25 (citation omitted).)

[46] The proposed wording of the 2007 and 2009 amendments defined invalidating prior art as that which is "patented, described in a printed publication, or in public use, on sale, or otherwise available to the public." (See id. at 25–27.)

the bill should have removed any "patent-forfeiture provisions that apply only to non-public prior art." (See id. at 27.) Defendant argues that this objection thus indicates that Senator Kyl was aware that the phrase "otherwise available to the public" still included secret prior art. (See id.)

Plaintiffs state that the Defendant attempts to minimize the sponsoring Senator's statements but "do[es] not cite a single statement from any congressperson that either rebuts the portions of the legislative history that Plaintiffs cite or affirmatively supports their statutory interpretation." (See dkt. 236 at 10.) Plaintiffs also note that Defendant cannot point to any support for its position in the Committee Report, "[d]espite its importance to statutory interpretation . . . ." (See id. at 12.) Plaintiffs claim that Defendant's arguments regarding prior patent reform bills are "based on mischaracterizations . . . and misleading inferences . . . ." (See id.) Plaintiffs clarify that only the 2007 patent reform bill "purpor[ted] to 'maintain' the pre-AIA on-sale bar." (See id. at 13.)

4. Public policy considerations

Plaintiffs argue that the AIA's overhaul of the United States patent system, i.e., converting from a first-to-invent to a first-inventor-to-file system, comports with the policy underlying the changes to the on-sale bar. (See dkt. 209 at 24–25.) Plaintiffs note that under the prior first-to-invent system, "there was a need to prevent an inventor from commercially exploiting the invention substantially beyond the statutory term through first conducting secret sales or offers for sales, and then filing a patent application." (Id. at 25.) Under the first-to-invent system, the on-sale bar deterred "an inventor's attempt to

commercialize his invention beyond the statutory term." (Id. (quotation and citation omitted).) The first-inventor-to-file system, however, adequately incentivizes an inventor to promptly apply for a patent because "the applicant risks having her invention patented by another that may have invented later." (See id. (quotation and citation omitted).)

Defendant critiques Plaintiffs' policy argument, stating that "this narrow view ignores the broader policy principles of the on-sale bar, which continue after the AIA." (See dkt. 226 at 31.) Defendant argues that the on-sale bar still functions as a deterrent for secret commercialization because "there is nothing inherent in a first-to-file system that will deter inventors from making use of their inventions as trade secrets and then some time later filing a patent application for the invention." (See id. at 32.) Defendant notes that Plaintiffs' proposed interpretation of § 102(a)(1), in which commercialization does not "affect[ ] the inventor's right to seek patent protection later," would have the opposite effect of encouraging secrecy. (See id.)

Plaintiffs maintain that the AIA's amendments reflect a significant shift in Congress's prioritization of certain policies underlying patent law. (See dkt. 236 at 14.) Plaintiffs argue, with respect to the Defendant's arguments that the first-inventor-to-file system has no effect on secret commercialization, that the AIA's prior-use defense allows "secret uses of one's proprietary technology." (See id. at 15.) Plaintiffs claim that the expansion of the prior-use defense enables secret uses without "forcing the first inventor to file a patent application" or "risk[ing] infringement under the 'first-inventor-to-file' system." (See id.) Thus, Plaintiffs contend, Congress intended the different provisions of the AIA to function together such that the

on-sale bar now applies only to "publicly accessible" prior art. (See dkt. 236-3 at 84 (AIA Committee Report) ("[T]he phrase 'available to the public' is added to clarify the broad scope of relevant prior art, as well as to emphasize the fact that it must be publicly accessible.").)

The Court, having considered the parties' arguments on the plain language meaning of § 102(a)(1), the USPTO's guidelines, the undisputed AIA Committee Report, and the public policy considerations underlying the passage of the AIA, concludes that § 102(a)(1) requires a public sale or offer for sale of the claimed invention. The new requirement that the on-sale bar apply to public sales comports with the plain language meaning of the amended section, the USPTO's interpretation of the amendment, the AIA Committee Report, and Congress's overarching goal to modernize and streamline the United States patent system. (See dkt. 236-3 at 83–84 (AIA Committee Report).)

2. Findings as to sale or offer to sell pre-AIA

The Court will now make findings on the "sale or offer to sell" prong as to the '724, '725, and '424 patents, which are subject to the pre-AIA on-sale bar. For purposes of the pre-AIA on-sale bar, the Court finds that the MGI Supply Agreement constitutes a sale because it was a contract for a future commercial product. See U.C.C. § 2–105(2) ("purported present sale of future good or of any interest therein operates as a contract to sell"). The fact that the clearly-described "products" had not yet received FDA approval at the time of the contracting does not change this conclusion. See Section II.A.3. Moreover, because the sale was made more than one year prior to the application date of the patents-in-suit, the MGI Agreement satisfies the pre-AIA sale prong under Pfaff. See

Pfaff, 525 U.S. at 67. The Court will now consider whether Helsinn's agreements with Oread and SP ("Oread and SP Agreements") also satisfy the sale prong of the pre-AIA on-sale bar.

a. Applicable legal standards

The Court notes that during the bench trial in this case, the Federal Circuit issued an opinion in Medicines Co. v. Hospira, Inc., 791 F.3d 1368 (Fed.Cir.2015), vacated by Medicines Co. v. Hospira, 805 F.3d 1357 (Fed. Cir. 2015), which addressed the issue of whether a sale for services constitutes a commercial sale under the pre-AIA on-sale bar. See id. at 1371. After closing arguments in this case, the Federal Circuit vacated its opinion in Medicines Co. and granted that plaintiff's petition for rehearing en banc. See Medicines Co., 805 F.3d at 1358. The Court notes that the issue of what constitutes a commercial sale under the pre-AIA on-sale bar remains in flux at this time. See id.

The facts underlying the district court's holding in Medicines Co. arose from ANDA litigation in which the ANDA applicant alleged, inter alia, that the patents-in-suit were invalid under the on-sale bar. See Medicines Co., 791 F.3d at 1370.[47] The Medicines Company hired Ben Venue to prepare batches of bivalirudin, a synthetic peptide used as an anticoagulant, "using an embodiment of the patented method." See id. at 1369. The batches were for both commercial and clinical packaging.

[47] A summary of the facts of Medicines Co. is provided in this Memorandum Opinion as the parties relied heavily on this case during their closing arguments. (See generally dkt. 353.) The prior ruling in Medicines Co. will be referenced by the Court only in the context of the parties' arguments.

See id. at 1370. The Medicines Company acknowledged that "each batch had a commercial value of over $10 million." See id. at 1371. The ANDA applicant alleged that the claimed invention was commercially offered for sale before the critical date. See id. at 1370. The district court found, inter alia, that the patents-in-suit were not invalid under the on-sale bar because: (1) the patentholder had only contracted with a manufacturing company for the sale of "manufacturing services"; and (2) the developmental batches manufactured under the agreement fell under the experimental use exception of the on-sale bar. See id. At issue on appeal is whether these facts constitute a commercial sale under the pre-AIA on-sale bar.[48]

The facts set forth in Medicines Co. are distinguishable from Trading Technologies International, Inc. v. eSpeed, Inc., 595 F.3d 1340 (Fed. Cir. 2010). In Trading Technologies, an inventor hired Trading Technologies ("TT") to build trading software in accordance with the inventor's idea. See Trading Techs., 595 F.3d at 1361. TT built the customized software and the inventor paid TT for this custom software. See id. The patent challenger ar-

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[48] The Federal Circuit requested briefing on the following issues:

> (a) Do the circumstances presented here constitute a commercial sale under the on-sale bar of 35 U.S.C. § 102(b)?
>
> (i) Was there a sale for the purposes of § 102(b) despite the absence of a transfer of title?
>
> (ii) Was the sale commercial in nature for the purposes of § 102(b) or an experimental use?
>
> (b) Should this court overrule or revise the principle in Special Devices, Inc. v. OEA, Inc., 270 F.3d 1353 (Fed.Cir.2001), that there is no "supplier exception" to the on-sale bar of 35 U.S.C. § 102(b)?

Medicines Co., 805 F.3d at 1358.

gued that the inventor's consulting agreement with TT invalidated the patent-in-suit under the on-sale bar. See id. The Federal Circuit held that the parties' consulting agreement was not a sale under the on-sale bar because "TT promised to develop trading software for [the inventor] because he lacked the technical expertise to do so." See id. The court held that "[i]nventors can request another entity's services in developing products embodying the invention without triggering the on-sale bar." Id. The court noted, in so holding, that an inventor's request to manufacture a product for "secret, personal use could not constitute a sale under 35 U.S.C. § 102(b)." See id.

"[A] sale is a contract between parties to give and to pass rights of property for consideration which the buyer pays or promises to pay the seller for the thing bought or sold." Bone Care Int'l, LLC v. Pentech Pharms., Inc., 2012 WL 1068506, at *6 (N.D. Ill. Mar. 29, 2012) (quoting In re Caveney, 761 F.2d 671 (Fed. Cir. 1985)). In Bone Care, the patentholder entered into a supply agreement with a manufacturer to produce batches of vitamin D_2 that the patentholder was "stockpiling for the purposes of commercialization after FDA approval of Bone Care's first NDA." Id. at *6. The court compared these facts to Trading Technologies, emphasizing that the contract "was not for services rendered . . . but explicitly set forth terms related to the sale of goods." Id.

b. Parties' arguments

Helsinn first argues that the Oread and SP Agreements were service contracts, in which Oread and SP provided services like manufacturing, formulation development, and analytical development to Helsinn. (See dkt.

353 at 96.) Helsinn analogizes this case to Trading Technologies, wherein the Federal Circuit held that inventors may request another entity to perform services without violating the on-sale bar. (See id.) See also Trading Techs., 595 F.3d at 1361. Helsinn asserts that its agreements with Oread and SP were similar in that they were for the development of products embodying the '219 patent. (See dkt. 353 at 98.)

Helsinn also argues that the Oread and SP Agreements were for developmental batches of its product, thus falling outside the "commercial sale" scope of the on-sale bar. (See id. at 97.) Helsinn distinguishes Medicines Co., noting that the commercial batches produced in Medicines Co. violated the on-sale bar because "[t]hey were stockpiled," marked with commercial numbers, and ready for shipping in anticipation of a launch. (See id. at 97–98.) Helsinn notes that the Oread and SP Agreements did not contemplate the purchase and sale of commercial batches; rather, the agreements were used "for clinical development, . . . stability testing," and other services "en route to seeking FDA approval." (See id. at 98.) Helsinn emphasizes that a pre-AIA analysis that invalidates patents based upon these developmental supplier agreements carries dangerous public policy implications because:

> Small companies like Helsinn rely extensively on contract manufacturing organizations during the development process of getting a pharmaceutical product to the market . . . . [I]f we are to invalidate patents based on use of CMOs [contract manufacturing organizations], there's going to be an awful lot of pharmaceutical patents that are in trouble out there that were never shown to work for their intended purpose during that developmental phase . . . .

(Id. at 99.)

Teva argues that the Oread and SP Agreements were "clearly binding commercial contracts" because the agreements set forth contractual terms like price and quantity. (See id. at 10–12.) Teva notes that Helsinn's interpretation of the Oread and SP Agreements as service contracts is tantamount to "characteriz [ing] any sale of a product as a service contract." (See id. at 12.) Teva relies upon the Federal Circuit's holding in Medicines Co., although as this Court has noted, the Federal Circuit vacated this opinion after the parties' closing arguments in this case. Teva also notes that Bone Care is instructive in this case as the court held that the supply agreement between the parties "was not for services rendered . . . but explicitly set forth terms related to the sale of goods." *Bone Care*, 2012 WL 1068506, at *6. (See also dkt. 353 at 30.)

With respect to Helsinn's argument that the on-sale bar does not apply to contracts for development batch manufacturing, Teva asserts that Helsinn has "expressly stipulated that they are not asserting the experimental use doctrine." (See dkt. 353 at 21; see also dkt. 317 at 2.) Teva also notes that the on-sale bar does not provide any "carve out for . . . CMOs or development agreements." (See dkt. 353 at 21.) Teva argues that in similar cases where the company did not have the manufacturing ability to develop its own drug product, such as Bone Care and Medicines Co., the courts found that these agreements qualified as "sales" under the on-sale bar. (See id. at 30.)

c. Analysis

The only issue that this Court will address in this subsection is whether the Oread and SP Agreements constitute a commercial sale or offer for sale under the pre-AIA on-sale bar. See 35 U.S.C. § 102(b). The Court, taking into consideration the parties' arguments and the unsettled law in this area, finds that the Oread and SP Agreements are not sales or offers for sale under the pre-AIA on-sale bar.[49]

The nexus of the parties' disagreement lies in whether the stockpiling for development processes like clinical trials one year prior to a patent's critical date constitutes a commercial sale or offer for sale under the on-sale bar. Helsinn argues that contracts that supply a company with its developmental batches for clinical trials and data-gathering cannot be considered a commercial sale or offer for sale. (See, e.g., dkt. 353 at 99.) Teva counters that Helsinn seeks to carve out a novel exception to the on-sale bar, and that "paying to have the product made . . . is starting to convert his invention into something that can be commercialized . . . ." (See id. at 21; id. at 30.)[50]

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[49] The Court agrees with Teva that Helsinn's argument that the Oread and SP Agreements were merely service contracts invites a slippery slope analysis in which this Court declines to engage. (See dkt. 353 at 12 ("[Y]ou could characterize any sale of a product as a service contract.").)

[50] Although not briefed by the parties, the Federal Circuit's rehearing en banc of Medicines Co., particularly on the issue of whether a supplier exception to the on-sale bar exists, may be instructive in these pharmaceutical patent cases with facts analogous to this case or Medicines Co. This Court cannot, however, read the tea leaves on the outcome of the Medicines Co. rehearing and will not do so here.

The sparse case law on this issue is distinguishable in part from this case, although the Court does bear in mind some similarities.[51] Unlike Trading Technologies, Oread and SP Agreements were not entered into for the purpose of Helsinn conducting its own "secret, personal use" of its product. See Trading Techs., 595 F.3d at 1362. But, similar to Trading Technologies, the Court finds that these agreements were not for the commercialization of Helsinn's product. (See dkt. 322 at 125, 129.) Unlike Bone Care, the Oread and SP Agreements were not entered into for the purpose of stockpiling a commercial product while anticipating FDA approval and a commercial launch. See Bone Care, 2012 WL 1068506, at *3. This case is similar to Bone Care in that both Bone Care and Helsinn lacked their own manufacturing capacity, and Helsinn's acknowledgement that the developmental batches were "commercial" in size is comparable to developmental batch "stockpiling." (See dkt. 312 at 19–20.)

The Court reverts back to the Pfaff test, which requires a claimed invention to be the subject of a "commercial offer for sale." See Pfaff, 525 U.S. at 67. There is no dispute that Helsinn and Oread, and later Helsinn and SP, entered into binding contracts for the manufacture of developmental batches of palonosetron, including "commercial scale" batches to satisfy NDA requirements. But the Court finds nothing in these agreements to suggest the contracts contemplated a commercial sale of any of those batches. (See, e.g., dkt. 322 at 125, 129.) Unlike Bone Care, Helsinn was not stockpiling its commercial product, or anticipating a launch with those batches pending FDA approval. See Bone Care, 2012 WL 1068506, at *6 (quotation

[51] As noted above, the Court is not considering the Federal Circuit's prior ruling in Medicines Co. for purposes of this analysis.

omitted) ("Bone Care was stockpiling for the purposes of commercialization after FDA approval of [its] first NDA."). Rather, Helsinn entered into the Oread and SP Agreements for the purpose of pursuing FDA approval, which includes, as Dr. Calderari testified, "analytical development, formulation development, batches preparation for clinical trials, and stability data generation." (Dkt. 322 at 122.)

The Court also finds compelling Helsinn's argument that many pharmaceutical companies rely upon the outsourcing of developmental batch manufacturing before the commencement of clinical trials. (See dkt. 353 at 99.) While the on-sale bar is intended to prevent the commercial exploitation of a patent prior to its critical date, the Court does not see how supply agreements for developmental batches can reasonably be considered commercial exploitation when, particularly in the pharmaceutical field, the developmental batches are critical to pre-commercialization steps, like clinical trials, formulation development, and manufacturing quality requirements. See, e.g., D.L. Auld Co. v. Chroma Graphics Corp., 714 F.2d 1144, 1147 (Fed. Cir. 1983). (See also dkt. 322 at 122.) In this case, the Court finds a marked difference between the commercial stockpiling in Bone Care and the developmental batches that were manufactured in this case.

The Court finds, for the above-stated reasons, that the Oread and SP Agreements do not constitute sales under the pre-AIA on-sale bar.

3. Findings as to sale or offer to sell post-AIA

As this Court has interpreted the post-AIA on-sale bar, the "sale" prong of the on-sale bar is satisfied by a public sale or offer for sale of the claimed invention. See,

e.g., 35 U.S.C. § 102(a)(1) (barring patentability if "the claimed invention was patented, described in a printed publication, or in public use, on sale, or otherwise available to the public").

The Court has found in Section II.A.2 that the Oread and SP Agreements were not "sales" under the pre-AIA on-sale bar. The Court further finds that the Oread and SP Agreements were not "public" sales under the post-AIA standard, because they were entirely subject to and performed under confidentiality restrictions. See Sections I.C.4 and I.C.8.

The Court will next consider whether the MGI License Agreement and the MGI Supply Agreement (collectively, "MGI Agreement") satisfies the post-AIA on-sale bar sale prong.

a. Legal standard

An agreement that "relates specifically to [a] supply of . . . worldwide requirements for what are clearly commercial purposes . . . constitutes an offer to sell that has been accepted." Enzo Biochem, Inc. v. Gen–Probe, Inc., 424 F.3d 1276 (Fed. Cir. 2005) ("Supply of worldwide requirements at reasonable times and prices surely means commercial supply . . . ."). In Enzo, the patentholder entered into an agreement that provided, "Enzo shall supply to Ortho and Ortho shall purchase from Enzo for use in Licensed Products no less than ninety percent (90%) of Ortho's United States requirements or seventy-five percent (75%) of Ortho's worldwide requirements of Active Ingredients . . . ." Id. at 1279.

Enzo argued that the agreement was vague and did not require Ortho to purchase the patent's embodiment

exclusively from Enzo. See id. at 1282. The patent challenger alleged that the agreement "created the necessary contractual obligations on the parties to constitute a commercial offer for sale." Id. at 1281. The Federal Circuit held that:

> Enzo's claimed invention, the polynucleotide probe, is a tangible item or product that can be sold or offered for sale. The language of that provision clearly imposes upon Enzo the obligation to sell and on Ortho the obligation to purchase a significant percentage of its U.S. and worldwide requirements of the product labeled "Active Ingredients." There is no doubt that paragraph 2.14 constitutes a binding commitment by the parties to enter into a commercial sale and purchase relationship.

Id.

The Federal Circuit also emphasized that Enzo's emphasis of the context of this particular sale provision was inapposite and "d[id] little to alter the plain language of that provision in the agreement." See id. at 1282.

The determinative factor under the sale prong of the on-sale bar is the contractual language of the agreement. See generally Apotex, Inc. v. Cephalon, Inc., 2011 WL 6090696 (E.D. Pa. 2011). In Apotex, the patentholder entered into a supply and license agreement in which its supplier had the "right to sell modafinil, a pharmaceutically active compound . . . and Cephalon wishes to purchase the Compound from Lafon." Id. at *15. The court found that the agreement's language was analogous to the Enzo agreement in that both provided for a "free supply of product for clinical testing," and "contain[ed] language akin to a requirements contract," including "to purchase"

and "to sell." Id. at *16. The court also noted that any mention of research and development in the contract was "incidental to the primary commercial purpose of the contract . . . ." See id.

Conversely, an agreement may not be considered a sale or offer for sale under the on-sale bar if the agreement lacks material terms that are common to commercial documents. See Elan Corp. v. Andrx Pharms., Inc., 366 F.3d 1336 (Fed. Cir. 2004). In Elan, the patentholder sent letters to various entities stating that Elan was seeking a partner in planning clinical studies. See id. at 1337–38. The letter also discussed granting a license and a pricing structure without any specific price term. Id. at 1341–42. The product at issue in Elan, a formulation of naproxen for the treatment of inflammation and pain, had not yet been patented or received FDA approval at the time of the letters being sent. See id. at 1337. The Federal Circuit concluded that there was no offer for sale in the letters because "an offer to enter into a license under a patent for future sale of the invention covered by the patent when and if it has been developed . . . is not an offer to sell the patented invention that constitutes an on-sale bar." Id. at 1341. The court noted that the letter did not contain "any mention of quantities, time of delivery, place of delivery, or product specifications beyond the general statement that the potential product would be a 500 mg once-daily tablet containing naproxen." Id.

b. Parties' arguments

Helsinn first argues that the on-sale bar does not apply because the MGI Agreement was indefinite as to the product that was going to be manufactured. (See dkt. 353 at 100–01.) The MGI Agreement defined "Products" as

"the pharmaceutical preparations for human use in I.V. dosage form containing the Compound as an active ingredient in the formulation that will be described in the Registration. . . ." (DTX-115-0007.) Helsinn analogizes this case to Elan, arguing that in both cases, the product was unspecified at the time the agreement was formed, and it was unclear as to whether a product actually existed at the time of the alleged offer for sale. (See dkt. 353 at 102.) Helsinn would distinguish Enzo from this case, arguing that "[t]he product at issue in [the Enzo] agreement was real. It was tangible. It was set in concrete." (See id.)

Helsinn next argues that the MGI Agreement never made the claimed invention available to the public prior to the critical date, thus never triggering the on-sale bar. (See dkt. 209 at 29; dkt. 353 at 87–88.) Helsinn argues as a threshold matter that the on-sale bar requires disclosure of the claimed invention, rather than the fact that a sale has merely occurred or will occur. (See dkt. 353 at 88.) Helsinn asserts that in order for a claimed invention to become available to the public and trigger the on-sale bar, the "very specific set of claim limitations" must be disclosed. (See id.)

Here, Helsinn notes that the MGI Agreement was executed in private and contained confidentiality provisions. (See dkt. 209 at 30.) Helsinn argues that its press releases and MGI's Form 8-K filed with the Securities and Exchange Commission were redacted and only contained information that "two parties [we]re working on the palonosetron product." (See dkt. 353 at 88.) Helsinn also emphasizes that the press releases and the Form 8-K failed to "disclose[ ] any aspect of the claimed invention of the '219 patent other than the use of the active ingredient palonosetron, which was already known in the prior art." (See

dkt. 209 at 30.) Helsinn concludes that because the claimed invention itself, i.e., Helsinn's palonosetron formulation, was never made available to the public, the on-sale bar has not been satisfied as it relates to the MGI Agreement. (See id.)

Teva argues that the MGI Agreement constitutes a sale or offer for sale under the on-sale bar. (See dkt. 353 at 18–19.) Teva first argues that the language of the agreement, on its face, requires a finding that the agreement is a requirements contract "that easily satisfies the Pfaff requirement of a 'commercial offer for sale.'" (See dkt. 226 at 35; see also dkt. 353 at 18.) In support of its contention, Teva notes that the MGI Agreement includes contract terms for product, quantity, and price for the "sale of Helsinn's palonosetron product that is an embodiment of the asserted claims of the '219 patent." (See dkt. 226 at 35.)

Teva also asserts that this case is analogous to Enzo insofar as Helsinn argues that the uncertain product defined in the MGI Agreement negates applicability of the on-sale bar. (See dkt. 353 at 19.) Teva notes that the Federal Circuit, in Enzo, summarily dismissed the patentholder's vagueness argument because the contract imposed "upon Enzo the obligation to sell and on Ortho the obligation to purchase . . . ." See Enzo, 424 F.3d at 1282. Teva argues that the language of the MGI Agreement, regardless of the definition of Helsinn's palonosetron product, set forth contractual terms under which both parties were bound. (See dkt. 353 at 18.)

With respect to Helsinn's threshold argument, i.e., that every claim limitation of the claimed invention must be made available to the public for a sale or offer for sale to satisfy the on-sale bar, Teva states that this "is not the

law now, and has never been." (See id. (citation omitted).) Teva argues that even under the post-AIA on-sale bar, the MGI Agreement invalidates the '219 patent because: (1) MGI was a member of the public at the time of the agreement; and (2) MGI's Form 8-K "discloses Helsinn's binding commercial sales agreement with MGI for the palonosetron product." (See dkt. 226 at 39–40.)

Teva first argues that "[t]he Federal Circuit has repeatedly held that for purposes of the on-sale bar, the 'public' is broadly defined and includes an independent party, not controlled by the seller, entering into an arms-length sales agreement for the later-patented good." (Id. (citations omitted).) Teva argues that because MGI is an independent entity and entered into an agreement with Helsinn, the sale was therefore available to the public. (See id. at 39.) Moreover, Teva asserts that MGI's Form 8-K "makes clear" that Helsinn had contracted to supply MGI's requirements for the palonosetron product for a price, so that MGI could in turn resell that product. (See id. at 40.) Teva notes that the "Product" disclosed in the MGI Agreement "embodies each of the asserted claims of the '219 patent," which satisfies the sale prong of the on-sale bar. (See id.)

c. Analysis

The Court is not persuaded by Helsinn's argument that the on-sale bar does not apply because the product defined in the MGI Agreement was indefinite or uncertain because it had not yet received FDA approval. (See dkt. 353 at 100–02.) The Court is guided by Enzo and Apotex, in which the Federal Circuit held that the sale prong of the on-sale bar is satisfied if an agreement between parties is for a commercial purpose (i.e., a sale or offer for

sale) and contains contractual language. See Enzo, 424 F.3d at 1282; Apotex, 2011 WL 6090696, at *16.

Here, Helsinn and MGI entered into a Supply and Purchase Agreement for the sale of Helsinn's commercial palonosetron product. (See dkt. 226 at 14.) The MGI Supply Agreement contained contractual terms relating to Helsinn's product, the quantity of product that would be sold to MGI, and at which price. (See id. at 35.) It is inapposite that at the time of the agreement, the product was uncertain and awaiting FDA approval, because the appendices to both the MGI License Agreement and the MGI Supply Agreement specified the exact dosages and concentrations that were in the pending FDA filings. See Section I.C.9. (See dkt. 353 at 100–02.) Indeed, under a pre-AIA analysis, the Court's analysis would end here with a conclusion that the MGI Agreement constituted a contract for sale, thus satisfying the "sale" prong of the on-sale bar.

However, the post-AIA on-sale bar also requires that the sale or offer for sale make the claimed invention available to the public. See 35 U.S.C. 102(a)(1) (barring patentability if "the claimed invention was patented, described in a printed publication, or in public use, on sale, or otherwise available to the public before the effective filing date of the claimed invention"). It is not sufficient that a sale or offer for sale merely occur.[52]

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[52] This Court is further bolstered by the USPTO's interpretation of the post-AIA on-sale bar, in which the USPTO concluded, "the sale must make the invention available to the public." See Examination Guidelines for Implementing the First Inventor to File Provisions of the Leahy–Smith America Invents Act, 78 Fed. Reg. 11,059, 11,075 (Feb. 14, 2013) (to be codified at 37 C.F.R. 1).

The Court finds that the MGI Agreement did not make the claimed invention available to the public. Teva asserts that the Form 8-K and Helsinn's press releases made the existence of the agreement available to the public. (See dkt. 226 at 40–41.) However, MGI's Form 8-K was redacted and indicated only that Helsinn and MGI had entered into an agreement to purchase Helsinn's product. (See, e.g., dkt. 226 at 14.) Additionally, Helsinn's press releases only disclosed the existence of the agreement between Helsinn and MGI. (See id.) Insofar as these documents publicized the parties' MGI Agreement, Teva is correct. But the post-AIA on-sale bar inquiry is not focused on the public disclosure of the sale or offer for sale; rather, the "sale" prong of the on-sale bar requires that the sale make the claimed invention available to the public one year prior to its critical date. Teva has failed to show how MGI's Form 8-K or Helsinn's press releases on the MGI Agreement made Helsinn's claimed invention, i.e., its palonosetron formulation, available to the public. See Section I.A.9.

The Court finds, for the reasons stated above, that the post-AIA on-sale bar does not apply to the MGI Agreement because the sale or offer or sale did not make Helsinn's claimed invention available to the public one year prior to the critical date.

4. Findings on ready for patenting

The Court, having considered the "sale" prong of the on-sale bar under both pre-AIA and post-AIA standards, will now consider whether the patents-in-suit were ready for patenting by the critical date of January 30, 2002. See Pfaff, 525 U.S. at 67–68. The parties agree that the "ready

for patenting" prong under Pfaff has remained unchanged by the AIA. (See dkt. 353 at 37, 119.)

a. Legal standards

In Pfaff, the Supreme Court held that an invention may be ready for patenting in two ways: (1) "proof of reduction to practice before the critical date;" or (2) "by proof that prior to the critical date the inventor had prepared drawings or other descriptions of the invention that were sufficiently specific to enable a person skilled in the art to practice the invention." See Pfaff, 525 U.S. at 67–68. To demonstrate reduction to practice, a party must prove that the inventor (1) "constructed an embodiment or performed a process that met all the limitations" and (2) "determined that the invention would work for its intended purpose." Z4 Techs., Inc. v. Microsoft Corp., 507 F.3d 1340 (Fed. Cir. 2007).[53] As patents are presumed valid, the patent challenger must prove by clear and convincing evidence that the claimed formulation was ready for patenting at the time of the critical date. See SRAM Corp. v. AD-II Eng'g, Inc., 465 F.3d 1351 (Fed. Cir. 2006).

Whether a claimed formulation has been reduced to practice is a fact-driven analysis that may require an analysis of the parties' claim construction. See, e.g., Mitsubishi Chem. v. Barr Labs., Inc., 435 Fed. Appx. 927, 934–35 (Fed. Cir. 2011); Allergan, Inc. v. Sandoz, Inc., 2011 WL 1599049 (E.D. Tex. Apr. 27, 2011). In Mitsubishi, the district court interpreted the claim "pharmaceutical composition for injection" to mean "a composition that is suitable

[53] The Court will focus on whether the claimed invention was reduced to practice, i.e., shown to work for its intended purpose, as this was the central issue disputed by the parties. (See, e.g., dkt. 353 at 37; id. at 102.)

for treating medical conditions by injection." Mitsubishi, 435 Fed. Appx. at 934 (quotation omitted). The patent challenger argued on appeal that the claim should have been interpreted as "a medicinal drug composition that can be administered by injection." See id. The patent challenger cited precedent in which the Federal Circuit had construed the term "pharmaceutical" to mean "medicinal drug." See id. (citing to Novartis Pharms. Corp. v. Eon Labs Mfg., Inc., 363 F.3d 1306 (Fed. Cir. 2004)). The court distinguished Mitsubishi from Novartis, noting that the claim limitation at issue in Novartis was a preparation claim and thus did not apply to the composition claim at issue in Mitsubishi. See id. The court further noted that "[c]laims to pharmaceutical compositions are typically distinct from claims to medicinal compounds themselves." See id. (internal quotation omitted). The Federal Circuit affirmed the district court, noting that "[t]he specification does not require this restrictive construction, nor is this property necessary for patentability." Id.

In Allergan, the parties disputed whether the claim construction at issue should include the additional limitation of "with a drug that meets FDA standards for approval." See Allergan, 2011 WL 1599049, at *8. The patent challenger argued that "in the United States, a patient cannot be legally treated with a drug that is not approved by the FDA." Id. The district court found that "it would be improper to read this limitation into the claims," because "FDA approval is irrelevant to proceedings before the [PTO]." See id.; see also AstraZeneca v. Apotex, 633 F.3d 1042 (Fed. Cir. 2010) (noting that, in an induced infringement case, the FDA's opinion regarding a proposed label amendment was inapposite because "the FDA is not the arbiter of patent infringement issues").

In other cases, a factual determination as to whether a formulation was ready for patenting, i.e., reduced to practice, may hinge on the timeline and completion of the formulation's clinical studies. See, e.g., In re Omeprazole Patent Litig., 536 F.3d 1361 (Fed. Cir. 2008) ("The district court found that the claimed formulation was not reduced to practice before the clinical trials were completed, and we uphold that finding."); Estee Lauder Inc. v. L'Oreal, *S.A.*, 129 F.3d 588 (Fed. Cir. 1997) ("[W]hen testing is necessary to establish utility, there must be recognition and appreciation that the tests were successful for reduction to practice to occur."); Bayer Schering Pharma AG v. Barr Labs., Inc., 2008 WL 628592, at *44 (D.N.J. Mar. 3, 2008) ("The extensive clinical testing demonstrates that there was a lack of confidence that the efficacy of the claimed invention could be based solely on the European trials."), aff'd on other grounds, 575 F.3d 1341, 1346 (Fed. Cir. 2009) (stating the "adverse rulings"—concerning the ready-for-patenting prong of the on-sale bar—were not cross-appealed).

In Omeprazole, the claimed formulation that was the subject of the underlying ANDA litigation was created in 1979. See Omeprazole, 536 F.3d at 1372. At that time, the inventors tested various formulations in order to "create a dosage suitable for commercialization," which included Phase II and Phase III trials. See id. at 1372–73. The patent challenger asserted that the patentholder's clinical trials violated the on-sale bar because "it was known in 1979—the year Astra filed its first patent application for omeprazole—that omeprazole could provide a safe and effective treatment." See id. at 1375.

The district court found that the patentholder's Phase III formulation was not reduced to practice because the

inventors had stated that the formulation only "might solve" problems associated with the formulation in earlier clinical trials. See id. at 1373. The district court noted that at the conclusion of Phase III trials, the formulation "still required extensive clinical testing and real-time stability testing to determine whether it could treat gastric acid diseases safely and effectively." Id. at 1373–74. The Federal Circuit affirmed the district court, noting that "[t]he existence of the formulation . . . does not establish that . . . the invention would work for its intended purpose." See id. at 1374–75.

Even if a formulation's clinical trials are fully completed and analyzed, the formulation may not be considered ready for patenting if the completed clinical trials studied a different patient population. See Bayer, 2008 WL 628592, at *43. In Bayer, the patent challenger asserted that the patentholder's claimed invention was invalid because it was in public use, i.e., reduced to practice, during European clinical trials, prior to the patent's critical date. See id. at *13. Unlike the case before this Court, the patentholder maintained that the United States ("U.S.") clinical trial was an experimental use. Id. at *38. Bayer asserted that its U.S. clinical trials were experimental because: (1) it was unknown whether the formula would be effective in the U.S. population; (2) the U.S. subjects were "far more diverse" than the subjects in the European trials; and (3) it was unknown how the test results between U.S. and European trials would differ. See id.

The court noted in its analysis that the European trials found that "both medications were shown to be effective oral contraceptives." Id. at *42. However, Bayer's experts testified that "the U.S. clinical trials were necessary to de-

termine whether the formula would be effective as an ovulation inhibitor in the U.S. population," citing the populations' differences in "weight, smoking/alcohol habits, and ethnic backgrounds." See id. at *43. The court noted that in Omeprazole, there was insufficient evidence of a reduction to practice because at least one clinical trial had not yet been analyzed. See id. The court held that in the present case, the patent challenger had not shown by clear and convincing evidence that the U.S. clinical trials were not necessary to show the formulation's safety and efficacy. See id. at *44. Accordingly, the court found that "[t]he extensive clinical testing demonstrates that there was a lack of confidence that the efficacy of the claimed invention could be based solely on the European trials." Id.

b. Applied legal standards

The Court will first address the parties' legal analyses of the ready for patenting prong of the on-sale bar. The Court will then address the parties' factual arguments as to whether Helsinn's claimed formulation was ready for patenting before the critical date.

1. Parties' arguments

Helsinn argues that its claimed formulation's treatment-like limitation—"to reduce the likelihood of [CINV]"—renders the Omeprazole holding even more applicable to the case before this Court. (See dkt. 353 at 116-17.) Helsinn notes that the limitation at issue in Omeprazole was a "pure formulation claim," which is a "less compelling" case for a court to require completed Phase III clinical testing. (See id.) Unlike Omeprazole, where the parties had full results from one Phase III

study, Helsinn notes that it only had preliminary, unanalyzed Phase III clinical trial results as of January 30, 2002. (See id. at 117.) Helsinn asserts that its treatment limitation makes this a unique case that goes beyond the facts asserted in Omeprazole, and requires fully completed and analyzed Phase III clinical trials to determine whether the invention was effective and ready for patenting. (See id.)

Teva argues that "courts regularly distinguish between patentability and FDA approval." (See id. at 54–55.) In terms of claim construction, Teva highlights Mitsubishi, noting that in that case, the Federal Circuit refrained from equating the term "pharmaceutical" with the FDA classification "safe, effective, and reliable for use in humans." (See id. at 54.) Teva argues that the court so held because FDA approval is irrelevant to a patentability analysis. (See id. at 54–55.)

Teva also argues that Omeprazole is irrelevant because the issue in that case was whether the Phase III formulation was stable. (See id.) Teva notes that Helsinn has stipulated to its claimed formulation's stability, and the only issue on this prong of the on-sale bar is the formulation's efficacy. (See dkt. 317 at 2.) Teva argues that Omeprazole does not address how fully analyzed and completed Phase III clinical trials are instructive to an efficacy analysis. (See dkt. 353 at 55.) Moreover, Teva notes that nowhere in Omeprazole does the Federal Circuit state that "FDA standards must be met before an invention is ready for patenting." (See id. at 56.)

1. Expert opinions

Dr. Fruehauf

Teva presented opinion testimony of Dr. John Fruehauf on the "ready to patent" prong of the on-sale bar issue. Dr. Fruehauf is an M.D. clinical oncologist with a Ph.D. in pharmacology who teaches, conducts clinical trials, and practices oncology at University of California Irvine and its comprehensive cancer center. He was accepted to testify as an expert in the clinical sciences and pharmacology, with a focus on oncology and supportive care. (Dkt. 324 at 4–14.)[54]

Dr. Fruehauf testified that in his opinion, a person of ordinary skill in the clinical sciences would know as of January 30, 2002 that palonosetron administered to a human reduces the likelihood of CINV. (Id. at 30–31.) The key documents that he discussed in support of that opinion he listed as follows:

- the Phase II 2330 study records;
- the July, 1998 Helsinn Clinical Meeting Minutes;
- the November, 1999 proposed Phase III protocols Helsinn sent to the FDA;
- the September, 2000 Helsinn press release announcing the Phase III start;
- the Phase III study documents; and

[54] Each of the experts who appeared in this trial was eminently qualified to provide the testimony they offered. The Court was highly impressed with each of their credentials and explanations of their opinions, and it was an honor and a pleasure to have them at the trial.

- a declaration later filed with the USPTO [not in the same patent family history] addressing invention timing issues ("Cantoreggi declaration").

(Id. at 33–34.)

Addressing the Phase II study 2330 records, Dr. Fruehauf referred to the text and a table in the Final Report of that study dated July 1995, DTX-0227-0005. He said the design of the study was "a very strong design for a Phase II trial." (Dkt. 324 at 36.) He summarized that the basic objective of the study, as stated in the text, was to determine whether palonosetron, over a dose range of 1 to 90 micrograms per kilogram, given to patients receiving highly emetogenic chemotherapy, would reduce the likelihood of CINV. The primary endpoint to be studied was complete control at 24 hours, defined as no nausea and no vomiting. A secondary endpoint studied was called "complete response," meaning no vomiting but some nausea reported. He pointed to the stated conclusion:

> Palonosetron, administered as a single IV injection of 3, 10, 30 or 90 μg/kg . . . was effective in suppressing [CINV] for 24 hours. All four doses were approximately equally effective as compared with the combined results from a cohort of 0.3 and 1 μg/kg.

(Id. at 37.)

Dr. Fruehauf discussed the Complete Control figures in the table presented with that study 2330 conclusion, which is shown here in the margin.[55] He stated that in his opinion, if a person of skill in clinical sciences were to see this Syntex data as of 1995, "it would be clear that the drug at the .25 mg dose [equivalent to 3 mcg/kg in the table] reduced the likelihood of nausea and vomiting." (Id. at 42–44 (bracketed text added).)

He was questioned by counsel for Helsinn about that table, and acknowledged that the "Complete Control" line — the primary endpoint of the study — showed there was no statistically significant difference between results for the bottom doses of 0.3-1 mg and any of the higher doses, including the 3 mcg/kg [0.25 mg] dose, except the 30 mcg/kg [2.1 mg] dose indicated with an asterisk. He said, "[t]hat is correct from a statistical perspective." (Id. at 130–34.) He also confirmed his awareness that in general, the FDA will not allow an indication to be claimed for a drug without a showing of statistical significance of an outcome for the primary efficacy endpoint of a study. (Id.)

He was also asked if he knew that the Syntex Formulation Book, as a result of all the analyses of the Phase II

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Parameters	RS-25259 Dose (μg/kg)				
	0.3-1	3	10	30	90
% Complete Control (24hrs)	24	46	40	50	46
%CompleteResponse (24 hours)	24	39	40	48	46
Median time (hours) to Failure (first emetic episode or rescue Rg)	5.6	22.7	19.0	>24*	21.8*

*statistically significant differences ($p<0.05$) vs. lowest dose group

(DTX-0227-0015.)

studies in May of 1995, recommended a palonosetron dose of 1 milligram for Phase III CINV trials. He said he was not aware of that fact. (Id. at 145–46, citing DTX-0254 and DTX-1023.)

Dr. Fruehauf was also shown the FDA's comments and instructions in the March 10, 1999 meeting with Helsinn, where the FDA said "[d]ue to a lack of dose response in this study, these data are inadequate to serve as pivotal efficacy support," and the FDA allowed Helsinn to re-analyze the 2330 data using historical controls in order to offer it as "supportive data" for efficacy. (Id. at 137–38.) He said in his opinion the FDA made a mistake about that; he said, "I think it [the 2330 study] did have a dose response. I think it was just a misunderstanding on the part of the [FDA] reviewer. . . ." (Id. at 137–38, 198–99 (bracketed text added).)[56] He explained that in his view, because the lowest doses showed low effect (albeit not in statistically significant numbers), and because the next four doses were all equivalent, that was a dose response. (Id. at 198–99.)

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[56] Here the Court notes that a close review of the 1995 Final Report of the 2330 study shows that the subsequent re-analysis resulted in an Errata statement added to that Report after the re-analysis of the data was conducted and reported in the PALO-00-01 Final Report. The Errata statement, dated August 12, 2002, reported that the table shown in the 1995 Final Report of the 2330 study, see n. 55 supra, was actually erroneous because the lines for Complete Control (the primary endpoint) and Complete Response (the secondary endpoint) were reversed. (DTX-0227-0012, -0013.) Thus, looking at the second line of data in the table, which is the actual data for Complete Control according to the Errata, there is not even one statistically significant figure, as shown by the lack of any asterisk in that second line of figures. Of course, Helsinn and the FDA did not know this fact on March 10, 1999 at the "End of Phase II" meeting, or when Helsinn submitted its proposed Phase III protocols dated November 15, 1999.

The next document Dr. Fruehauf discussed in support of his opinion was the July 1998 Helsinn Clinical Meeting Minutes, reflecting the week-long meeting in Palo Alto, CA attended by scientists from Helsinn, the former Syntex, and consultants including Dr. Gandara. See n. 17 supra and accompanying text. There, the outcome of the meeting was to further study doses of 0.25, 0.75 and 2.0 mg, and corresponding concentrations in a 5 ml solution, for possible use in the Phase III trials. (DTX-0015-0008, -0009.)

Dr. Fruehauf interpreted those discussions to indicate that Helsinn at the time regarded the 0.25 dose as the minimum effective dose, "and they were going to take that with a couple of other doses that were higher into the Phase III study." He also said he agreed with Dr. Gandara's recommendation that "3μg/kg was most likely the correct dose for CINV." (Dkt. 324 at 48–49, citing DTX-0015-0008, -0012.) His basis for that opinion was "[b]ecause I think it's clear from the [Phase II] trial that the .25 milligram dose was the inflexion point, and after that you've saturated the receptors and that that's the minimally effective dose, and you want to avoid higher doses because, as you go up on doses, you're more likely to get side effects." (Id. at 50 (bracketed text added).)

On cross-examination, Dr. Fruehauf agreed that the stated outcome of the 1998 Helsinn Clinical Meeting was to keep the 2.0 mg dose in the selected group, and that dose was equivalent to the 30 mcg/kg dose that was shown as the only statistically significant dose in the Phase II 2330 study primary endpoint data. (Id. at 154–55.) He also acknowledged that although he routinely participates in clinical trials in his medical work, he has never been personally involved in the selection of a specific dosage of a

drug in a treatment that was eventually approved by the FDA. (Id. at 111–12.)

Dr. Fruehauf also relied upon his reading of the proposed Phase III protocols that Helsinn submitted to the FDA dated November 15, 1999. (DTX-0293.) He referred to the statement that "[d]ata from [the 2330] study clearly demonstrate that the 3 μg/kg dose of palonosetron is the minimal effective dose in preventing CINV." (DTX-0293-0035 (bracketed text added).) He stated that he agreed with this statement, which was based on the same data shown in the table in the 1995 Final Report (see n. 55 supra). He said that in his opinion, if a person of skill were to see this statement to the FDA, "[t]hey would interpret this statement as to indicate that the Phase II study showed that the .25 milligram dose could reduce the risk of nausea and vomiting." (Dkt. 324 at 55–56.) The version of that 2330 study table contained in the November 1999 Phase III protocols, however, carried forward the same lack of statistical significance for Complete Response for any dose except the 30 mcg/kg, equivalent to 2.0 mg, dose. (See DTX-0293-0034.)

Dr. Fruehauf also cited the Helsinn press release of September 14, 2000, announcing the commencement of the Phase III trials. There, the company said, "[t]he Phase II trials demonstrated the efficacy of Palonosetron in the prevention of emesis with no significant side effects. . . ." (Dkt. 324 at 56–57.) He said that in his view, a person of skill in the art would understand from this statement that Helsinn knew that palonosetron reduced the likelihood of emesis. (Id.)

He also recognized, however, that when the database from the earliest of those trials was unblinded but not fully analyzed at the other end of the Phase III trials in

January 2002, the Helsinn press release on January 16, 2002 said "[w]e are pleased to have completed all patient treatment and to have begun analysis of the data collected in the palonosetron clinical program." That press release said "The Phase 2 clinical trial results were promising, and we are hopeful that the Phase 3 Palonosetron data will demonstrate that it can make a difference for cancer patients suffering from CINV." (Id. at 182–83, citing DTX-0040.)

Dr. Fruehauf next discussed the fact that the "preliminary" data tables for PALO-99-03, dated January 7, 2002, which Helsinn sent to the FDA with its letter of February 7, 2002, turned out to be identical to the corresponding final data tables contained in the Clinical Study Report for that trial dated July 19, 2002. Teva's counsel asked him if it would be surprising that those results in the final report were identical to the preliminary analysis. He replied, "[t]hey have to be because this was the pre-stipulated result of the unblinded data which had been locked so it can't change." (Id. at 65.)

He said that fact supported his opinion "[t]hat we have a clear understanding from a Phase II study that .25 was the minimal effective dose that was carried forward into Phase III, and in the Phase III trial, that .25 milligram dose was very effective at reducing the likelihood of CINV in a prospective randomized trial. . . . Prospective is you plan it in advance, and you do what you plan to do, and you can't change what you plan to do." (Id.) He did not deny, however, that as of January 7, 2002, the figures Helsinn had in hand were preliminary figures only. (Id. at 66.)

The last document relied upon by Dr. Fruehauf for his opinions was a declaration filed by Helsinn in the USPTO on Sept. 2, 2010, in support of a patent application that

was not part of the same patent family history as the patents-in-suit, but it did relate to a proposed method of treatment claim for acute and delayed CINV using a 0.25 mg dose of palonosetron. The first declarant listed was Helsinn executive Sergio Cantoreggi, and the other two declarants were company owners Enrico and Riccardo Braglia. (DTX-0287-0413 ("Cantoreggi declaration").) It stated that Alberto Macciocchi, who was the project manager for the PALO-99-03 study, was then deceased, and the purpose of the declaration was "to establish that Alberto Macciocchi, Enrico Braglia and Riccardo Braglia had conceived the idea to use palonosetron for the treatment of acute and delayed-onset CINV, and had conducted clinical trials in humans to test this idea, at least as early as October 2, 2001." (Id.)

Referring to the Clinical Study Report for PALO-99-03 dated July 19, 2002, attached to the declaration as Exhibit A, the Cantoreggi declaration stated, inter alia:

> 2) We submit this declaration to establish that Alberto Macciocchi, Enrico Braglia, and Riccardo Braglia had conceived the invention defined by claim 1 of this application, and reduced it to practice, before November 16, 2001, the date that Dr. Piraccini published abstract no. 5169 in Blood, vol. 98, no. 11 part 2.
>
> 3) In particular, we submit this declaration to establish that Alberto Macciocchi, Enrico Braglia, and Riccardo Braglia had conceived the idea to use palonosetron for the treatment of acute and delayed-onset CINV, and had conducted clinical trials in humans to test this idea, at least as early as October 2, 2001.
>
> . . . .

> 17) Thus, we had conceived the idea to use 0.25 mg. palonosetron for the treatment of acute and delayed-onset CINV, as described in claim 1, at least as early as August 1, 2001 (the date that the study began).
>
> 18) Most important, we had successfully tested the method in human patients, and we had done so before October 2, 2001 (the date the study was completed).
>
> 19) As reported on page 8 of Exhibit A,
>
> "Pairwise testing revealed differences between palonosetron 0.25 mg and ondansetron in favor of palonosetron 0.25 mg. for . . . number of emetic episodes on Study Days 1, 2, 3 and the time period 0 to 120 hours . . ."

(DTX-0287-0413, -0415.)

Dr. Fruehauf testified that his reading of this declaration indicates that Helsinn was saying that "they knew the result, they knew that .25 milligrams was effective to reduce the risk of chemotherapy-induced nausea and vomiting, by October 2nd, 2001." (Dkt. 324 at 71.) The reference to October 2, 2001 is, of course, the "last patient out" date, as stated on the first page of the Clinical Study Report for PALO-99-03 dated July 19, 2002, which was attached to the declaration as Exhibit A. (See DTX-0287-0418.) Dr. Fruehauf opined that in his experience, saying that they had "successfully tested the method in humans . . . before October 2, 2001," would mean "that they had some understanding from the result of the study and that it was successful." (Dkt. 324 at 72.)

He gave his theory about how Helsinn could have asked the CRO conducting the clinical trial to do some calculations of broad averages in the blinded data before that "last patient out" date, stating that a person of ordinary skill could do the same calculations if they had access to the data. (Id.) On cross-examination, he said he himself did not know what "reduced to practice" meant in the declaration because it is a legal term, so he would not know how those declarants interpreted that term. (Id. at 157–58.) He also said that his theory about Helsinn possibly having obtained broad efficacy information about the blinded data prior to the "last patient out" date of October 2, 2001 was not supported by any evidence and was just his speculation. (Id. at 164–65.)

Dr. Fruehauf further testified that the inactive excipients in the Phase III formula would not impact the efficacy of the 0.25 mg dose when administered to a patient. Therefore, he said, if a person of ordinary skill in the clinical sciences understood that the Phase II formulation with 0.25 mg was effective for CINV, he or she would expect the Phase III formulation to behave in a similar fashion. (Id. at 84.)

The ultimate opinion expressed by Dr. Fruehauf was stated as follows:

> I think it would be clear to a person of skill in the clinical arts, based on the Syntex Phase II study, [and] based on unblinded data analysis of PALO-99-03 where that output was January 7th, and Cantoreggi's declaration that would potentially rely on blinded data, that it was clear that the .25 milligram dose reduced the likelihood of chemotherapy-induced nausea and vomiting.

(Id. at 89 (bracketed text added).)

Dr. Fruehauf also stated that he disagreed with the opinions stated by Helsinn's expert, Dr. Peck, to the effect that one would need two prospective randomized blinded trials, fully analyzed, to know that the 0.25 mg dose reduced the risk of CINV as claimed in the '219 patent. He said he considered FDA criteria and Patent Office criteria to be different. He again stated that in his opinion, on the strength of the Phase II study as confirmed in the first Phase III study, it was clear that the 0.25 mg dose was effective for that purpose. (Id. at 93.)

Dr. Peck

Helsinn presented opinion testimony of Dr. Carl Peck on the "ready to patent" prong of the on-sale bar issue. Dr. Peck is an M.D. with board certifications in internal medicine and in clinical pharmacology who also had a Fulbright fellowship in physical chemistry and a research fellowship in clinical pharmacology focused on pharmacokinetics and biostatistics and involving clinical trials. For many years he was in the U.S. Army, practicing medicine and researching and teaching. That service included founding the division of clinical pharmacology at the Uniformed Services University of Health Services, a military medical school in Washington, D.C.

He was next recruited to become the director of the FDA Center for Drug Evaluation and Research, CDER, where he served for six years and was personally involved in reviewing numerous INDs and NDAs.[57] Next he went

[57] While serving as director of CDER, Dr. Peck was also named Assistant Surgeon General of the United States. (Dkt. 337 at 11.)

to Georgetown University as a professor of pharmacology, founding the Center for Drug Development Science and consulting with companies. He is currently consulting and is designated as a "special government employee" available to consult with the FDA. He was accepted to testify as an expert in scientific standards regarding determinations of the efficacy and safety of pharmaceutical drug products. (Dkt. 337 at 4–16).[58]

Dr. Peck testified with reference to the asserted limitations of the patents-in-suit claiming a formulation intended for IV administration to a human to reduce the likelihood of CINV. He stated that in his opinion, a POSA in the relevant time period would require "fully analyzed results of two adequate and well controlled Phase III studies" in order to determine that a drug formulation would be effective for reducing the likelihood of CINV. (Id. at 22.) It was further his opinion that the pharmaceutical formulations relevant to the patents-in-suit "were not known to work for their intended purpose of reducing the likelihood of CINV in human patients" before January 30, 2002. (Id. at 78.)

Dr. Peck gave three reasons for his opinions. First, the results of a single Phase III trial would not be sufficient for a POSA to know that the drug was efficacious. Second, assuming that the results of a single Phase III were sufficient, the preliminary results from such a study would provide only insufficient information. Third, under the "impossible hypothetical" that Phase III trials were not needed in this case, the Phase II 2330 study as reported

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[58] Teva did not object to Dr. Peck being admitted to testify as offered, but did express a relevance issue with his testimony. (Dkt. 337 at 20.)

"provided only a signal," and the FDA itself said it was insufficient as a pivotal trial, so that would also not be sufficient to convince a POSA of efficacy. (Id.) He added that a pharmaceutical formulation could not be used for IV administration to a human to reduce the likelihood of CINV without FDA approval, except under an active FDA-approved IND. (Id. at 24.)

He stated that the standards he employed were scientific standards that he thinks a POSA (as defined by plaintiffs) would embrace. He explained that "[t]hese are standards that have been developed by a consensus of scientists over many decades. Since FDA is a science-based agency and . . . uses science all the time in its review and guidance and decisions," he referred to FDA standards in forming his opinions in this case. (Id. at 24.) He testified that the FDA is very highly regarded as a scientific and regulatory agency, stating, "I think scientists in the industry and scientists in the academic community recognize that those standards are their standards." (Id. at 26–27.)

Dr. Peck testified that with regard to clinical trials, the FDA sets the standards, and it provides guidance. Importantly, he said, it has "articulated a statistical framework for being able to really know from the data, particularly data that's highly variable, that a drug is working." (Id. at 26.)

Addressing Dr. Fruehauf's reliance on Phase II data in his opinion testimony, Dr. Peck commented that "Phase II studies, with a few exceptions, are never capable of permitting a POSA to really know that the drug will be effective in the broad range of patients that will be candidates for the drug if and when the drug is actually approved." (Id. at 33.) He explained the reasons included that those studies are typically small, they are often very limited in

the type of patients, and they often produce confusing results. (Id. at 33–34.)

Contrasting the purpose and structure of Phase II trials with that of Phase III trials, Dr. Peck described Phase III trials as follows:

> [T]he basic standard for knowing that a drug will work, and one that you can generalize to all patients that would be candidates in the future, are the Phase III trials. These are defined as adequate and well controlled, meaning they're large. They're structured with sound statistical principles. There is a wide range of patients . . . so that they are representative. And they're positioned, also, to provide a much richer collection of data that will be important to the prescriber and to the patient that can be articulated in the prescribing information, the so-called drug label.

(Id. at 34.)

He also explained the reason why two Phase III trials are generally necessary to know whether a pharmaceutical product would work for its intended purpose, which is replication. "[S]cientists always know that one experiment is not necessarily reproducible . . . . [T]he basic, good science requires replication. So you need at least two." (Id.) He said that 40 to 60 percent of Phase II trials that advance to Phase III do not result in approved drugs because one or more of the trials will fail. (Id.) He added that a typical Phase III program in 2003 and at present, as illustrated by the Phase III trials in this case, are done in different centers by different investigators around the world, so there is independence in the replication design.

He said that a drug such as palonosetron would not qualify for a single Phase III trial to get FDA approval. (Id. at 37.)

Dr. Peck reviewed the same Phase II 2330 study documents on which Dr. Fruehauf had testified. Looking at the Final Report of that study dated July 1995, Dr. Peck testified that this was one of five Phase II studies. He said it was "an exploratory dose-ranging study . . . . And the purpose of this was to evaluate graded doses to evaluate the safety and to identify a possible signal of benefit." (Id. at 39–40.) He noted that it was a small study; most of the patients were male and none had received a chemotherapeutic agent before; and "that was quite unrepresentative of any broader population." (Id.)

Looking at the data in the summary table of the 2330 Final Report, see n. 55 supra, Dr. Peck did point out that in the entire table there were only two findings of statistical significance, and both of them were at the 30 mcg/kg level. He also stated that there was no "ordered dose response," because even the stated results for 3 to 90 mcg/kg were 46, 40, 50, and 46. He was asked whether that could indicate that an efficacy plateau was reached at the 3 mg/kg [0.25 mg] level, and he said that was only one hypothesis that could arise from that raw data. Indeed, he said, in the other Phase II studies that were done, the best dose was one of the others. (Id. at 40–44.)

Focusing on the difference in results between the 24% figure for the lowest +. 3 to 1 mcg/kg dose and the 46% result for the 3 mcg/kg dose, he said that might or might not indicate efficacy, stating, "[t]he scientific method, the agreed-upon approach in drug studies, is to couple an apparent difference with a statistically significant difference so that if you were to repeat this trial, you would get the

same result . . . . I really can't conclude anything from the 24 versus 46 because this could change in the next study. It's too small a study." (Id. at 44–45.)

Dr. Peck also reviewed the minutes of the March 10, 1999 meeting of Helsinn with the FDA. He stated that the names of FDA representatives included the CDER division director, the medical team leader, and the medical officer (primary reviewer on the product) -- all of whom were M.D.'s, as well as two pharmacologists and a chemist. He chaired many such meetings himself, he said, and has been to many more since leaving his CDER director position in 1993. (Id. at 52.)

He highlighted the various portions of those minutes where the FDA communicated that the Phase II 2330 study data "did not show a convincing dose-response pattern." As he characterized that discussion at the meeting:

> FDA says, well, look, first of all, there's a lack of dose response in that study, so, therefore, we really can't entertain that data set, as is, to support. However, there is a possibility—and this is implied in the future, there is a possibility—that the data itself may be useful as supportive data. So, this is basically a "no," that study is insufficient.

(Id. at 55.)

He also reviewed the re-analysis report of the 2330 study data that the FDA permitted Helsinn to use as support for its pivotal Phase III study PALO-99-05, PTX-182. He said it was a lengthy report that made adjustments to the data, then constructed an "historical placebo" comparator [the study itself was not designed with a placebo], and did a statistical analysis of all that data. "And with those

adjustments," he said, "it turns out that the +.25 milligram and the +.75 . . . both of them were statistically significantly different from this historical placebo, which permitted then the revised data, and analysis, to be viewed by FDA to be adequate to support the already available Phase III trial [referring to PALO-99-05, the HEC trial] that had demonstrated effectiveness." He noted the date of that re-analysis report in August 2002, well after the critical date of January 30, 2002. (Id. at 57–60 (bracketed text added).)

Addressing Helsinn's April 7, 2000 letter to the FDA submitting the November 15, 1999 proposed protocols for the three Phase III studies, Dr. Peck highlighted the contents in those documents where Helsinn said the Phase II results "suggested" efficacy, and that the Phase III trials were designed "to support the hypotheses" that palonosetron was not inferior to existing setrons. He said, "the key word here is 'hypothesis'. We don't know. If they knew, they would have filed a new drug application. They know that more studies have to be done and they're requesting permission to undertake three new . . . Phase III studies." (Id. at 49.)

Dr. Peck described the three full-scale Phase III trials as all using an historical placebo control model, as well as two different comparators (ondansetron and dolasetron), and large numbers of patients at different centers. He said those were "three adequate and well-controlled Phase III clinical trials." Only the first of those three, the PALO-99-03 study, was unblinded before January 30, 2002. (Id. at 60–69.)

The sequence of events after the "last patient out" date of October 2, 2001, reflected in the Clinical Study Report for PALO-99-03, was reviewed and explained by Dr.

Peck. See Section I.C.10. In response to Dr. Fruehauf's discussion of the Cantoreggi declaration and his "hypothetical" analysis of the pre-October 2, 2001 blinded data theorized by Dr. Fruehauf, Dr. Peck said he thought it would be impossible to try to guess what the efficacy outcomes were, even if the sponsor could get access to the data; nor were there any such requests reflected in the study records. (Id. at 69–70.)

Dr. Pecks's explanation of the major analytical process necessary, according to the PALO-99-03 protocols, before and after the "unblinding date" of January 2, 2002, is described above in Section I.C.10.

Referring to the Helsinn letter of February 7, 2002, transmitting to the FDA "the preliminary data for Complete Response," Dr. Peck said "the author of that letter knew exactly what he was saying. This is preliminary. This is not final. And we're just showing you a couple tables." (Id. at 76.)

Dr. Peck said that the tables attached to that February 7, 2002 Helsinn letter to the FDA were one of probably 300 tables that were under analysis at the time, and the table is expressly represented as preliminary data. He said that to evaluate the data reliably, one would need all of the supporting information and more statistical data, as was done for the final Clinical Study Report dated July 19, 2002. He said that although there is no indication that the raw data of the study was changed after the "locked" date, there was at least one amendment to the statistical analysis plan on December 13, 2001. (Id. at 165–66.)

He also did not agree with Dr. Fruehauf that there were no potential differences in the Phase II and Phase III efficacy results based on the different formulations

used in those studies, referring to the saline-based solution in Phase II and the full pharmaceutical formulation in Phase III. He said the buffers differed in their constituents, and the pH was different in the two sets of studies. "So these are fundamentally different formulations," according to him. (Id. at 46.)

3. Analysis

Proof that a claimed formulation has been reduced to practice requires clear and convincing evidence that the inventor (1) constructed an embodiment that met all the limitations, and (2) determined that the invention would work for its intended purpose. Z4 Techs., Inc., 507 F.3d at 1352. Whether the formulation claimed in the patents-in-suit in this case was reduced to practice hinges on the timeline of testing and the knowledge that a person of ordinary skill would have developed in light of the historical facts. Id.

Here, the issue is whether such person would likely know that the claimed intravenous pharmaceutical formulation containing palonosetron was effective for reducing the likelihood of emesis or CINV in a human as of the critical date of January 30, 2002. The Court finds that there is not clear and convincing evidence to establish this prong of the on-sale bar test for patent invalidity. Taking in order the documents relied upon by Teva and its expert on this point, the Court makes the following factual findings. Citations to all the testimony and exhibits on these points are contained in the preceding sections of this opinion. We will use the fixed dose measure in this discussion, e.g., 0.25 mg, rather than the weight-based measure, e.g., 3 mcg/kg, shown in some of the records.

The Phase II 2330 study data, as reported in the Final Report of that study dated July 1995, showed no statistical significance in the stated primary endpoint of Complete Control for 24 hours for any dosage below 2 mg. While the 2330 study was a well-designed Phase II study for its purpose, it lacked the scope and controls that would make it a valid prediction of efficacy at any dose. The FDA so informed Helsinn at the March 10, 1999 "End of Phase II" meeting, and the Court finds that was a scientifically valid observation that a POSA would make when viewing that documentation. Syntex, which presided over all four of the completed Phase II palonosetron trials, ended its research by recommending in its Formulation Book that Phase III use a 1.0 mg dose for CINV.[59]

When Helsinn took over the palonosetron development project and assembled its project team of scientists, and advisors, they struggled long and hard to predict a possible minimum effective dose to take to Phase III trials. Even the highly respected clinician Dr. Gandara, who consulted at the week-long Helsinn Clinical Meeting in July 1998, could only posit that he thought 0.25 mg was "most likely" the correct dose for CINV. He was far superior to being an person of ordinary skill in the art, but that is how he viewed the problem at that time.

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[59] The Court finds further verification that the Final Report of the 2330 study was not as reliable as it would need to be in the fact, not brought out in the evidence at trial, that the very table that summarized the primary endpoint data was wrong and mixed up the results of the primary and secondary endpoints—a fact that was only discovered in the intensive re-analysis study PALO-00-01 suggested by the FDA. See n. 56 supra.

All present at that July 1999 Helsinn Clinical Meeting recognized that Phase III testing was essential to determine the efficacy and correct dosage of palonosetron in a completed pharmaceutical formulation for CINV. The fact that the outcome of that meeting in 1998 was a decision to continue to consider doses of 0.25, 0.75 and 2.0 is also a reflection of the uncertainty, in their view, of the results that might be obtained in Phase III. As Dr. Calderari also testified, even when he and Dr. Macciocchi continued debating the tradeoff between dosage and likely stability, Dr. Macciocchi still wanted to include a much higher dosage than 0.25 or 0.75 in Phase III.

The November 1999 proposed Phase III protocols, submitted to the FDA on April 7, 2000, made numerous statements of hopeful expectation about the 0.25 and 0.75 doses proposed for the trials. Nevertheless, the fact that Helsinn elected to test the two doses, including 0.75 mg, even though it would be a more cumbersome and expensive endeavor, reflected Helsinn's concern that it had no assurance of the efficacy at the 0.25 level. Helsinn was aware, as it stated there, that its "hypotheses" were to be tested in Phase III. Helsinn's statement in the same document that it was "clear" that 0.25 was the minimum effective dose was just one among many less confident statements in the proposal. Likewise, Helsinn's press release statement, at the start of patient enrollment for the trials, that "the Phase II trials demonstrated the efficacy" of the drug was in the nature of a marketing piece rather than any statement of scientific knowledge. Again, in context, the fact that Phase III trials were commencing meant that Helsinn had no such knowledge at that time.

This Court is also not persuaded that the "preliminary" unblinded data of the earliest Phase III study,

PALO-99-03, shown in the three tables dated January 7, 2002, sent to the FDA on February 7, 2002, informed Helsinn or a POSA that the 0.25 mg dose was effective for CINV, which was the only kind of emesis that was even studied at the Phase III level. Those tables were generated a mere five days after the Phase III data was "unblinded," and less than three weeks after the data was "locked" on December 19, 2001. More than six months of additional analytical work lay ahead at that time, leading to the final Clinical Study Report dated July 19, 2002. Indeed, there had already been one amendment to the statistical design of the study on December 13, 2001, and more amendments to the analytical process were entirely possible in the months to follow.[60]

The fact that the summary tables of preliminary data dated January 7, 2002 did not undergo change in their contents during that analytical period, and that data was the same in the final Clinical Study Report as of July 19, 2002, does not in the view of the Court establish that the preliminary results were final. Quite the contrary; it would seem that in view of the changes in methodology that were entirely possible during the analytical period (as experts on both sides agreed), a POSA would not have been surprised at all to see those values change between the preliminary and the final numbers. The Helsinn press release on January 16, 2002 was consistent with that understanding, saying, "[w]e are pleased to have completed all patient treatment and to have begun analysis of the data." See n. 36 supra.

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[60] Another indicator of the fluidity of the analytical process during that period, although not addressed by the witnesses at trial, is seen in the section of the PALO-99-03 Clinical Study Report entitled "Additional changes after unblinding," quoted in n. 38 supra.

The Cantoreggi declaration did state factual truth, based on the historical evidence that the declarants were reconstructing for that PTO submission. It was in an unrelated patent family history, but the Court has carefully considered its content as relevant to the "ready to patent" issue here. The factual content of that declaration states that "we had conceived the idea to use 0.25 mg. palonosetron for the treatment of acute and delayed-onset CINV . . . as least as early as August 1, 2001 (the date that the study [PALO-99-03] began)." "[W]e had successfully tested the method in human patients, and we had done so before October 2, 2001 (the date the study was completed)." (DTX-0287-0415 (bracketed text added).) Both of those facts were literally true. But there is no evidence in this record that Helsinn knew or could have known, until the results of the study were processed, locked, unblinded, and fully analyzed, that those results were successful, nor did the declarants so state. As for the declaration statement that the invention had been "reduced to practice" before November 16, 2001, that was not a statement of historical fact but a use of legal language to support an ultimate factual conclusion at best, and is not binding upon this Court in analyzing the factual issues here.

Teva's expert, Dr. Fruehauf, opined that the results of the Phase II 2330 study, coupled with the preliminary results of the Phase III PALO-99-03 study, were sufficient to have informed a POSA that palonosetron was effective to reduce the likelihood of CINV (which is emesis, as claimed in the first three patents-in-suit), and also that the 0.25 dose of palonosetron was effective to reduce the risk of CINV as claimed in the '219 patent. This Court does not find that the evidence supports such a finding under the clear and convincing standard of proof that applies to this determination.

It is not necessary for the Court to make a further ruling as to whether, as Dr. Peck opined, fully analyzed results of two adequate and controlled Phase III studies were necessary in this particular case to establish the efficacy of the claimed palonosetron formulation. The date when the action stopped, for purposes of the on-sale bar in this case, was January 30, 2002. At that time there were no fully analyzed Phase III studies in this case. Further, as the Court has found, the Phase II data would have been wholly insufficient at that time to support any valid scientific knowledge of efficacy as claimed. Accordingly, for the reasons stated here, and based on all other historical facts described in Section I.C, the Court finds that the patent challenger has not shown by clear and convincing evidence that as of January 30, 2002, the inventor had determined that the invention would work for its intended purpose.

5. Conclusions as to on-sale bar claims

The Court has made the following findings and conclusions in this section, all directed to Teva's claim that the patents-in-suit are invalid under the on-sale bar provision of 35 U.S.C. § 102.

- The MGI Agreement was a "sale" under the pre-AIA. See Section II.A.2.
- The Oread and SP Agreements were not "sales or offers to sell" under the pre-AIA. See Section II.A.2.
- The MGI Agreement was not a "sale" under the AIA. See Section II.A.3.
- Defendant has not shown by clear and convincing evidence that as of January 30, 2002, the inventor had

determined that the invention would work for its intended purpose. See Section II.A.4.

B. Written Description

1. Legal standards

A patent must contain "a written description of the invention." 35 U.S.C. § 112(a). "[T]he hallmark of written description is disclosure." Alcon Research Ltd. v. Barr Labs., 745 F.3d 1180, 1190 (Fed. Cir. 2014). The disclosure must "allow one skilled in the art to visualize or recognize the identity of the subject matter purportedly described." Enzo Biochem, Inc., 323 F.3d at 968. The disclosure need not contain "either examples or an actual reduction to practice"; rather, the critical inquiry is whether the patentee has provided a description that "in a definite way identifies the claimed invention" in sufficient detail that a person of ordinary skill would understand that the inventor was in possession of it at the time of filing. Alcon Research, 745 F.3d at 1190–91. This is an objective inquiry "into the four corners of the specification." Ariad Pharm., Inc. v. Eli Lilly & Co., 598 F.3d 1336, 1351 (Fed. Cir. 2010). "A claim that recites a property that is necessarily inherent in a formulation that is adequately described is not invalid as lacking written description merely because the property itself is not explicitly described." Allergan v. Sandoz, Inc., 796 F.3d 1293, 1309 (Fed. Cir. 2015).

A patent is presumed valid, and this presumption can be overcome only by facts supported by clear and convincing evidence to the contrary. Enzo Biochem. Inc., 323 F.3d at 962.

2. Findings and conclusions on written description

Teva asserts that if the Court finds that fully complete Phase III data would be required as claim support in order for the '219 patent to be "ready for patenting" under the on-sale bar, then that patent is invalid for lack of written description because there is no Phase III data, or for that matter any preclinical or clinical efficacy data, in the specification. (Dkt. 312 at 34–35.)

Helsinn argues that the '219 patent specification does satisfy the written description requirement in that it does describe the claimed inventions, both as to formula and as to efficacy. Helsinn cites the formula embodiment described in the specification, "the palonosetron is supplied in vials that comprise 5 ml. of solution, which equate to about 0.25 mg of palonosetron at a concentration of about 0.05 mg/ml." (DTX-0268, col. 10, lines 7–8; see dkt. 311 at 39.) The efficacy information described in the specification is further cited on this point:

> Recently, clinical investigations have been made concerning palonosetron, a new 5-HT3 receptor antagonist reported in U.S. Pat. No. 5,202,333. These investigations have shown that the drug is an order of magnitude more potent than most existing 5-HT3 receptor antagonists, has a surprising half-life of about 40 hours, and is effective to reduce delayed-onset nausea induced by chemotherapeutic agents.

(DTX-0268, col. 1, lines 43–54; see dkt. 311 at 39–40.)

A second point emphasized by Helsinn is that the on-sale bar "ready for patenting" prong is measured on the date one year prior to the patent application filing date,

whereas written description information includes that intervening year and what a POSA would know from publicly available data as of the application date. (Dkt. 320 at 102.) Here, it is undisputed that between January 30, 2002 and January 30, 2003, there was at least one public disclosure of details about the clinical efficacy of the 0.25 mg dose. The PALO-99-04 study results were summarized, in an abstract presented by Helsinn's Dr. Macciocchi and researchers who worked on that trial, at a conference of the Multinational Association of Supportive Care in Cancer ("MASCC") on June 23–26, 2002 in Boston. (PTX-297.) See Section I.C.11.[61] Teva's expert Dr. Fruehauf agreed that the data shown in that Grunberg abstract supports the stated conclusion of the authors. (Dkt. 324 at 124–29.)

Finally, Helsinn argues that the Allergan decision "slammed the door" on the written description defense as asserted here, as the Federal Circuit held that a claim that recites a property that is necessarily inherent in the formulation is not invalid for lack of written description, even if such property is not "explicitly described." (Dkt. 353 at 152.)

The Court finds that the specification of the '219 patent provides an adequate written description of the efficacy of the invention claimed. See 35 U.S.C. § 112(a). The specification discloses the claimed formulations, and the Court finds that as of the provisional application date of

[61] The parties also agree that the published prior art in this case is defined under 35 U.S.C. § 102(b), so the operative date for published prior art relevant to obviousness is January 30, 2002, which is one year before the priority date of January 30, 2003. (Dkt. 328 at 240–41.) This published reference in June 2002 would not therefore qualify as § 102(b) prior art, but is relevant to what a POSA would know, for purposes of written description analysis, on January 30, 2003.

January 30, 2003, a skilled artisan "would immediately discern the claimed formulation in that disclosure." Moreover, actual data from the PALO-99-04 Clinical Study was publicized by Helsinn at the MASCC conference in June 2002. The Court is also persuaded by Allergan, which held that a property inherent to a claimed formulation is not lacking a written description merely because the property is not "explicitly described" in the specification. Id. Rather, the critical inquiry is whether the formulation itself is adequately described. See id.

Here, the Court is satisfied that Helsinn's claim for a palonosetron formulation "to reduce the likelihood of cancer chemotherapy-induced nausea and vomiting" is adequately supported by the written description in the specification. The Court finds that this description, especially in view of the June 2002 public disclosure, is adequate such that a skilled artisan would have knowledge that the inventors were in possession of the invention at the time of the patent application, and that there is no clear and convincing evidence to the contrary.

C. Infringement

1. Legal standards

Section 271(e)(2)(A) of the Patent Act provides that:

> It shall be an act of infringement to submit—(A) an application under section 505(j) of the Federal Food, Drug, and Cosmetic Act or described in section 505(b)(2) of such Act for a drug claimed in a patent or the use of which is claimed in a patent . . . .

35 U.S.C. § 271(e)(2)(A).

Under the Hatch-Waxman framework, the filing of an ANDA constitutes an artificial act of infringement for purposes of creating case or controversy jurisdiction. Ferring B.V. v. Watson Labs., Inc.-Fl., 764 F.3d 1401, 1408 (Fed. Cir. 2014) ("Ferring II"); see also Eli Lilly & Co. v. Medtronic, Inc., 496 U.S. 661, 676 (1990). This artificial, or technical, act of infringement does not in and of itself constitute a literal infringement. See Ferring II, 764 F.3d at 1408 ("The district court here thus erred to the extent that it read § 271(e) to mean that [defendant's] act of filing an ANDA, by itself, established infringement . . . ."). Indeed, once jurisdiction has been established by way of § 271(e)(2)'s technical act of infringement, "traditional patent law principles" control and a court must conduct a traditional infringement analysis. See id. This analysis requires a "comparison of the asserted patent claims against the product that is likely to be sold following ANDA approval . . . ." See id. Moreover, it requires the patentholder to prove the infringement of the asserted patent claims by a preponderance of the evidence. See Glaxo, Inc. v. Novopharm, Ltd., 110 F.3d 1562, 1567 (Fed. Cir. 1997) ("The plain language of the statute does not alter a patentee's burden of proving infringement, nor does it mandate an infringement analysis limited to the scope of the approval sought."). As will be discussed below, a court's analysis differs based upon whether the ANDA specification directly resolves the infringement question or is silent as to the infringement of asserted patent claims.

"[I]f a product that an ANDA applicant is asking the FDA to approve for sale falls within the scope of an issued patent, a judgment of infringement must necessarily ensue." Sunovion Pharms., Inc. v Teva Pharms., USA, Inc., 731 F.3d 1271, 1278 (Fed. Cir. 2013). In Sunovion, the

ANDA applicant requested approval of an amount of stereoisomer ranging from 0.0 to 0.6%. See id. at 1274–75. The patentholder argued that the ANDA specifications infringed its patent, which claimed a stereoisomer of "less than 0.25%." See id. at 1274. The Federal Circuit noted that while the filing of an ANDA itself "constitutes a technical infringement for jurisdictional purposes," a traditional infringement analysis is required to determine whether a court should enter a judgment of infringement. See id. at 1278. The Sunovion court looked to the ANDA specifications, as this was the "subject matter that determines whether infringement will occur." See id. The court held that the ANDA applicant's request for approval for an isomer amount of 0.0 to 0.6% fell squarely within the scope of the "less than 0.25%" limitation set forth in the asserted patent claims and entered a judgment of infringement. See id.

Conversely, "[i]f any claim limitation is absent from the accused device, there is no literal infringement as a matter of law." See Bayer AG v. Elan Pharm. Research Corp., 212 F.3d 1241, 1247 (Fed. Cir. 2000). The asserted patent claims at issue in Bayer involved a pharmaceutical composition with a specific surface area ("SSA") of 1.0 to $4m^2/g$. See id. at 1246. The ANDA applicant requested approval from the FDA of a bioequivalent product with a SSA of $5m^2/g$ or greater. See id.[62] The court noted that "[t]he focus under § 271(e)(2)(A), is on what the ANDA applicant will likely market if its application is approved, an act that has not yet occurred." See id. at 1248 (quotation and citation omitted). "[T]his hypothetical inquiry is

[62] The district court had also noted that the ANDA applicant's supplier did not sell the composition with a SSA under $4.7m^2/g$ in the United States. See Bayer, 212 F.3d at 1246.

properly grounded in the ANDA application and the extensive materials typically submitted in its support." See id. However, if the ANDA applicant requests approval of a "well-defined compound, then the ultimate question of infringement is usually straightforward." Id. at 1249. The Federal Circuit reasoned that because the applicant's ANDA specification included a compound which "cannot have a SSA of less than $5m^2/g$ . . . [the applicant] cannot literally infringe the '446 patent." See id.

"In cases in which the ANDA specification does not resolve the infringement question in the first instance, [the Federal Circuit has] endorsed the district court's reference to relevant evidence, including biobatch data and actual samples of the proposed generic composition that the ANDA filer had submitted to the FDA." Ferring II, 764 F.3d at 1409 (citing Glaxo, 110 F.3d at 1567); see also Ferring B.V. v. Watson Labs., Inc.-Fl., 764 F.3d 1382, 1387–88 (Fed. Cir. 2014) ("Ferring I") ("When an ANDA is silent with respect to infringement . . . the correct analysis is under Glaxo . . . , not Sunovion.").

In Glaxo, an ANDA applicant filed for approval of a crystalline compound ("Form 1"). See Glaxo, 110 F.3d at 1564. The ANDA also specified that "the marketed product [would] be approximately 99% pure Form 1 [of the compound]." See id. The patentholder for a different crystalline form ("Form 2") brought suit under § 271(e)(2), alleging that the ANDA applicant infringed its Form 2 patent claim. See id. The ANDA application did not explicitly address what amount of Form 2, if any, would be present in the approved product. See id. at 1566 (internal quotation omitted) ("The [district] court also found that the . . . evidence before it demonstrated in clear and con-

vincing fashion that Novopharm's product would not contain any Form 2 RHC1 and thus would not infringe . . . [the patents].").

The court acknowledged that because the "crystalline compound was capable of existing in multiple crystalline forms, or mixtures thereof, the ultimate question of infringement is not so simple." See id. at 1569. In its analysis, the court reiterated that "the statute [§ 271(e)(2)(A)] requires an infringement inquiry focused on what is likely to be sold following FDA approval." Id. at 1568. When the ANDA specifications do not directly resolve this inquiry, then all relevant evidence, including materials that the applicant submitted to the FDA, as well as the ANDA itself, should be considered by the court. See id. at 1568–70. The court noted that these materials include "actual samples" and "extensive technical data required by the FDA." See id. at 1569 n. 2. The Federal Circuit affirmed the district court's finding that the patentholder had failed to prove infringement by a preponderance of the evidence and noted that the court "properly considered the ANDA itself, the materials submitted by Novopharm to the FDA, and other pertinent evidence provided by the parties." See id. at 1570.

2. Findings and conclusions on infringement

a. Parties' arguments

Plaintiffs argue that there is "no genuine dispute that the CINV dosage strength in Defendants' respective ANDAs literally meets all of the limitations of the asserted claims of the '219 patent." (Dkt. 207 at 12.) Plaintiffs assert specifically that: (1) this Court should interpret § 271(e)(2)(A) as a substantive infringement test for Hatch-Waxman cases, as well as a jurisdiction-conferring

statute; (2) their position on ANDA infringement is supported by current Federal Circuit precedent; (3) Teva fails to cite any authority in support of its non-infringement position; and (4) Teva's characterization of the different dosage strengths as different products is inapposite to the infringement inquiry under § 271(e)(2)(A). (See, e.g., dkt. 207; dkt. 225; dkt. 237; dkt. 353 at 89–90.)

Plaintiffs argue as a threshold matter that § 271(e)(2)(A) is more than a "subject matter conferring statute" and should be interpreted as "the substantive test for infringement in these Hatch-Waxman Act cases." (Dkt. 353 at 90.) Plaintiffs assert that under AstraZeneca v. Apotex, 669 F.3d 1370 (Fed. Cir. 2012), the Federal Circuit held that § 271(e)(2)(A) "establishe[s] a specialized new cause of action for patent infringement." (Dkt. 207 at 12 (quotation and citation omitted).) This new cause of action "directs our analysis to the scope of approval sought in the ANDA." (Id. (quotation and citation omitted).) Plaintiffs argue that under AstraZeneca, "seemingly there should be no dispute here" because Teva has filed an ANDA requesting approval to sell a product in the CINV dosage strength. (Dkt. 353 at 90; see also dkt. 207 at 13–14.)

Plaintiffs next assert that their position is supported by current Federal Circuit precedent. (See dkt. 237 at 5.) Plaintiffs analogize this case to Sunovion, asserting that Teva's ANDA for the CINV dosage strength alone "satisfies the limitations of the asserted claims . . . regardless of whether approval is also sought for other dosage strengths of that product." (See dkt. 207 at 13.) Plaintiffs note that the Federal Circuit found that the ANDA applicant in Sunovion had infringed even though the applicant requested approval for isomers that fell outside of the

"less than 0.25%" asserted patent claim (i.e., 0.26% to 0.6%.) (See id.) Plaintiffs state that "[t]his is analogous to the two dose/volume values that are possible based upon the amount of otherwise identical 0.05 mg/mL palonosetron solution poured into the vials for each dosage strength." (Dkt. 237 at 6.) Plaintiffs distinguish this case from the Glaxo/Ferring line of cases, wherein the ANDA is silent as to the issue of infringement, and note that "if Defendants' approach were correct, then [the ANDA applicant in Sunovion] would have been permitted to sell the 0. 3-0.6% isomers . . . ." (See dkt. 225 at 9.)

Plaintiffs also argue that Teva has failed to cite to any authority in support of a finding of non-infringement of the '219 patent. (See dkt. 237 at 10.) Plaintiffs assert that Teva's citation of Ferring I and Ferring II as support for the application of a Glaxo analysis (i.e., looking to the product likely to be sold following ANDA approval) in this case, is misplaced. (See id. at 7–8.) Plaintiffs note that Ferring I and Ferring II clarified that the ANDA specification is central to any infringement analysis, and that a Glaxo analysis applies only when an ANDA is silent as to the asserted patent claims. (See id.)

Plaintiffs further argue that Teva's characterization of the CINV dosage strength and PONV dosage strength as different products is "immaterial, as it cannot be disputed that each of Defendants' ANDAs contains only one ANDA specification defining the scope of approval sought from the FDA." (Dkt. 225 at 5.)[63] Plaintiffs also note that Teva

[63] Plaintiffs asserted in their opposition memorandum that Teva amended its ANDA to remove the PONV dosage strength "i.e., the entire basis for its summary judgment motion." (See dkt. 225 at 6.)

"do[es] not even address the fact that they can remove the CINV dosage strength from their respective ANDAs, if desired." (See dkt. 237 at 9.)

Teva argues that (1) its PONV dosage strength does not meet "each and every limitation of the asserted claims;" and (2) that Plaintiffs have failed to show by a preponderance of the evidence that Teva's PONV dosage strength product infringes the '219 patent. (See dkt. 202 at 11; dkt. 234 at 7–8.)

Teva first argues that its PONV dosage strength does not meet "each and every limitation of the asserted claims." (Dkt. 202 at 11.) Plaintiffs' asserted patent claims "require a formulation that includes palonosetron hydrochloride in an amount of 0.25 mg based on the weight of its free base." (Id. at 12 (quotation omitted).) Teva notes that its PONV dosage strength includes a total drug content of only 0.075 mg of palonosetron hydrochloride based on the weight of its free base. (See id.) Teva asserts that "[a]s a matter of law, 0.075 mg cannot be equivalent to 0.25 mg." (Id. (citation omitted).) Moreover, Teva points out that the asserted patent claims require a formulation that has a 5 ml sterile aqueous isotonic solution, whereas Teva's 0.075 mg/1.5 ml product has a solution volume of only 1.5 ml. (See id.) Lastly, Teva notes that Plaintiffs' intended use language is "to reduce the likelihood of cancer chemotherapy-induced nausea and vomiting." (Id. at 13.)

Teva, in reply, denies amending its ANDA to remove the PONV dosage strength. (See dkt. 234 at 5–6.) Teva states that it has "always sought, and continues to seek, final marketing approval from the FDA for this product." (Id. at 6.) The Court will not address this argument as Teva has maintained that it did not amend its ANDA.

Teva argues that its PONV dosage strength product is labeled for the treatment of postoperative nausea and vomiting, and "thus cannot be equivalent." (See id.)

Teva asserts that Plaintiffs have failed to prove, by a preponderance of the evidence, that the PONV dosage strength product infringes the asserted claims under the '219 patent. (See dkt. 234 at 7–9.) Teva argues that Plaintiffs misconstrued the holding in Sunovion, noting that "the Sunovion court used the ANDA specification to define the product on which to base the infringement inquiry." (Id. at 8.) Teva emphasizes that its ANDA specification defines the product—0.075 mg/1.5 ml—and that "there is no question that the 0.075 mg/1.5 ml product, as described in Teva's ANDA, does not meet the limitations of the '219 patent." (See id. at 9.)

Teva further distinguishes *AstraZeneca* by noting that regardless of whether the Federal Circuit established a substantive test for infringement under § 271(e)(2)(A), the court nevertheless held that the patentholder failed to establish, by a preponderance of the evidence, that the ANDA applicant had infringed the asserted patent claims. (See dkt. 221 at 12.) Teva noted that AstraZeneca did not change the Federal Circuit's holding in Glaxo that § 271(e)(2) "does not alter a patentee's burden of proving infringement." (See id. (citing Glaxo, 110 F.3d at 1567).)

b. Analysis

The Court, having considered the parties' arguments, finds that Plaintiffs have not established by a preponderance of the evidence that Teva's 0.075 mg/1.5 ml product infringes the asserted claims of the '219 patent under § 271(e)(2)(A).

Plaintiffs argue as a threshold matter that § 271(e)(2)(A) not only establishes subject matter jurisdiction, but also sets forth the substantive test for infringement under Hatch-Waxman Act litigation. (See dkt. 353 at 89–90; see also dkt. 207 at 13.) Plaintiffs state that the Federal Circuit followed this very approach in AstraZeneca, in which the court held that § 271(e)(2)(A) "establishe[s] a specialized new cause of action for patent infringement." (See dkt. 207 at 12 (quotation and citation omitted).) In that case, the Federal Circuit agreed with AstraZeneca's jurisdictional interpretation of § 271(e)(2), but specifically held that "[w]hile the district court erroneously concluded that it lacked subject matter jurisdiction over AstraZeneca's claims, its judgment of dismissal was nevertheless correct, for we agree with the district court's underlying determination that AstraZeneca failed to state a viable claim for relief under § 271(e)(2)." AstraZeneca, 669 F.3d at 1377.

The Court finds that the holding in AstraZeneca does not overrule the Glaxo holding, i.e., that the infringement inquiry under § 271(e)(2)(A) "is the same as it is in any other infringement suit, viz., whether the patent in question is invalid or will not be infringed by the manufacture, use, or sale of the drug for which the [ANDA] is submitted." Glaxo, 110 F.3d at 1569 (quotation and citation omitted). Moreover, the burden to prove infringement remains squarely on the patentholder. See id. at 1567.

These principles are not limited to those Glaxo-like cases where the ANDA specifications do not resolve the infringement question. Rather, the Federal Circuit has applied this § 271(e)(2)(A) traditional infringement analysis regardless of whether the ANDA specification resolves the infringement inquiry. See, e.g., Ferring II, 764

F.3d at 1408 ("As we have explained, once jurisdiction is established, the ultimate infringement inquiry provoked by [an ANDA] filing is focused on a comparison of the asserted patent claims against the product that is likely to be sold . . . . "); Bayer, 212 F.3d at 1249 ("[T]he focus of the infringement inquiry under . . . § 271(e)(2)(A) is on the product that will be sold after the FDA's approval of the ANDA . . . . "). This Court will thus analyze Plaintiffs' § 271(e)(2)(A) infringement allegations under a traditional infringement analysis.

Here, Teva concedes that its 0.25 mg/5 ml CINV dosage strength product meets the limitations of the asserted claims of the '219 patent. (See dkt. 234 at 9.) However, this does not end the infringement inquiry. (See dkt. 353 at 90.) The Federal Circuit has instructed that the inquiry must focus on "a comparison of the asserted patent claims against the product that is likely to be sold." See, e.g., Ferring II, 764 F.3d at 1408. As Teva has already conceded that its CINV dosage strength product infringes the '219 patent, and leaving aside for the moment the parties' invalidity issues as to all four patents-in-suit, the only product that Teva is likely to sell is the PONV dosage strength. (See dkt. 234 at 9.) Thus, Plaintiffs must prove by a preponderance of the evidence that the PONV dosage strength product infringes the asserted '219 patent claims. See Glaxo, 110 F.3d at 1567.

Plaintiffs argue that there is "no genuine dispute that the CINV dosage strength in Defendants' respective ANDAs literally meets all of the limitations of the asserted claims of the '219 patent." (Dkt. 207 at 12.) While Plaintiffs analogize this case to Sunovion in that both applicants' ANDAs specify an infringing product, this case differs in that "Teva's ANDA specification also defines another

product—the 0.075 mg/1.5 mL product." (See dkt. 234 at 9.) See also Sunovion, 731 F.3d at 1279 (quotation and citation omitted) ("[A]n ANDA specification defining a proposed generic drug in a manner that directly addresses the issue of infringement will control the infringement inquiry."). Regardless of whether Teva conceded that one of its two proposed generic drugs infringed the '219 patent, the burden remains with Plaintiffs to prove that the remaining product in Teva's ANDA specification—the PONV dosage strength product—infringed the '219 patent by a preponderance of the evidence. Plaintiffs have failed to do so.

The Court, for the reasons stated above, finds that Teva's PONV dosage strength product (i.e., its 0.075 mg / 1.5 ml product) does not infringe the asserted claims of the '219 patent.

D. Defining the Person of Ordinary Skill in the Art

The obviousness analysis is conducted from the perspective of a person of ordinary skill in the prior art ("POSA"). 35 U.S.C. § 103(a). The same POSA features in the legal standards for the "ready to patent" prong of the on-sale bar under 35 U.S.C. § 102(a), and for written description under 35 U.S.C. § 112. See Sections II.A.4 and II.B.1. The Court is defining POSA here as it relates to the entire patent dispute.

The hypothetical person of ordinary skill "is presumed to be aware of all the pertinent art" at the time the invention was made. AstraZeneca Pharms. LP v. Anchen Pharms., Inc., Nos. 10–1835, 10–4203, 10–4205, 10–4971, 10–5519, 11–2483, 11–2484 (consolidated), 2012 WL 1065458, at *19 (D.N.J. Mar. 29, 2012) (citation omitted).

The person of ordinary skill "is also a person of ordinary creativity, not an automaton." KSR Int'l Co. v. Teleflex Inc., 550 U.S. 398, 421 (2007).

The POSA may be a composite of various types of individuals. See AstraZeneca Pharms., 2012 WL 1065458. At issue in AstraZeneca was the validity of a patent covering: (1) sustained release formulations of quetiapine, a compound useful as an antipsychotic agent; and (2) treatment methods that included "[a] method of treating psychotic states or hyperactivity in a warm-blooded animal which comprises administering to said . . . animal an effective amount of a formulation of [any one] of [the] claims." The AstraZeneca court defined the person of ordinary skill as a "clinician or an antipsychotic drug researcher," and a "formulation scientist." Each composite of the POSA took into account the educational level of the inventor and an active worker in the field, as well as the types of problems and solutions encountered in the art, the rapidity of innovation, and sophistication of the technology.

1. Expert testimony

Plaintiffs' expert Dr. Gordon Amidon testified at trial that he would define a POSA as an individual comprising the various facets of a "drug development team" including a pharmaceutical scientist, clinician, and formulation scientist. (See dkt. 342 at 147–48, 152 (sealed).) Dr. Amidon explained that a POSA composed of different fields was necessary because of the interdisciplinary nature of drug development. (See id. at 152.) He explained that a pharmaceutical scientist is necessary for the "physical chemistry and preformulation science" involved in drug development. (Id. at 153.) A clinician is required to establish "clinical parameters," i.e., the dose and the efficacy of the drug.

(Id. at 157.) Dr. Amidon also testified that while a formulation scientist would be involved throughout the entire drug development process, it is the formulation scientist's expertise that ensures a stable product and addresses any manufacturing issues that may arise towards the end of a drug development project. (Id. at 158–59.)

Dr. Amidon's testimony also touched upon the educational qualifications of a POSA. (See dkt. 342 at 148.) He testified that a POSA would have a degree in a chemistry-related field ("pharmaceutical chemistry," "pharmacy," "medicine," "clinical pharmacology," or "general pharmaceutical science") with a B.S., M.S., Ph.D., or M.D. The POSA, by way of incorporating the skill set of a pharmaceutical scientist, would have a knowledge of statistics as well. (See dkt. 342 at 147–48.)

Teva's expert, Dr. Lee Kirsch, proposed a hypothetical POSA as "a formulation scientist typically with a Ph.D. in pharmaceutics or a related field and would have a couple of years of experience in developing I.V. formulations." (Dkt. 326 at 19.) Dr. Kirsch also testified that a POSA would "collaborate with others of ordinary skill in the art" and would "draw upon the knowledge and expertise of clinicians and pharmacologists . . . . " (Id. at 20.)

2. Analysis

The parties do not seem to dispute that a POSA would have an advanced degree in a chemistry-related field, or alternatively, a bachelor's degree with a greater number of years of relevant experience. (Compare dkt. 342 at 148 (requiring "two, three, four years" of relevant experience "depending on the level of education"), with dkt. 326 at 19 (testifying that POSA would typically possess a Ph.D. in pharmaceutics or a related field and have "a couple of

years of experience" in developing I.V. formulations).) The parties also do not dispute that the POSA would include a formulation scientist. (See dkt. 326 at 19; dkt. 342 at 152.)

However, the parties disagree about whether the POSA also should include the knowledge and skills of a clinician or a pharmaceutical scientist, or whether it suffices that the formulation scientist "collaborates" with these individuals. (See id.) Helsinn contends that the POSA would take into account the interdisciplinary nature of drug development and would include both a clinician and pharmaceutical scientist into the POSA definition; Teva argues that the POSA is limited to the formulation scientist. (See id.)

We find merit in Plaintiffs' contention that the person of ordinary skill in the art would possess all the attributes of a multi-member drug development team. The '219 patent is not limited to formulation, but rather includes treatment-like methods as the Court has construed it. (See DTX-0268, col. 10, lines 1–38; dkt. 290.) The parties have stipulated to a similar construction of the claim preambles of the '724, '725, and '424 patents. (Dkt. 290 at 12.) Thus, the "pertinent art" of these patents includes the field of pharmaceutical science, i.e., selecting the API and using the physical chemistry of the API to match it to a delivery system, formulation, or dosage form; the field of clinical medicine, i.e., establishing the dosing, volume, safety, and efficacy of the drug product; and the field of formulation pharmaceuticals, i.e., creating stable formulations of the active pharmaceutical ingredient in preparation for manufacturing. (See dkt. 342 at 134–36, 152–59.)

Dr. Amidon's testimony on defining the POSA encompasses this entire drug development process and his hypothetical POSA included the various professionals and skill sets that are required during this process. (See id.) Conversely, Dr. Kirsch's hypothetical POSA did not consider crucial parts of the drug development process, such as selecting an API or dosage forms. (See dkt. 353 at 128.) As Helsinn argued at trial, Teva's POSA analysis runs afoul of Insite, wherein the Federal Circuit cautioned against an "overly narrow statement of the problem," as this can become a "prohibited reliance on hindsight." Insite Vision Inc. v. Sandoz, Inc., 783 F.3d 853, 859 (Fed. Cir. 2015). (See also dkt. 353 at 128.) Here, Dr. Kirsch's hypothetical POSA "is assigned a particular formulation problem" with issues such as "choosing active ingredients or dosage forms" already decided. (See id. at 128.)

Accordingly, the Court finds that a person of ordinary skill in the art pertinent to the '219 patent would include a pharmaceutical scientist, clinician, and formulation scientist. The pharmaceutical scientist and formulation scientist would have two to four years of relevant experience in their field, as well as an advanced degree in a chemistry-related field, discussed supra. The clinician would have experience in "the therapeutic area" that is the focus of the API, or in this case, treating humans affected by cancer chemotherapy-induced nausea and vomiting. (See dkt. 342 at 134.)

CONCLUSION

This Supplemental Opinion constitutes the Court's further findings of fact and conclusions of law, pursuant to Federal Rule of Civil Procedure 52(a), on the issues ad-

Animal Testing Legislation

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Presentation
New York State Bar Association
FD&C Section
January 17, 2019

Cosmetic Animal Testing
Proposed Federal and State Legislation

Sharon Blinkoff
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H.R. 6903 Safe Cosmetic and Personal Care Act of 2018 Introduced by Jan Schakowsky

Beginning on the date of enactment of this subchapter, it shall be unlawful for any entity to conduct, directly or pursuant to contract, animal testing for the purpose of developing a cosmetic for sale in or affecting interstate commerce.

"(b) LIMITATION ON CONSIDERATION OF DATA.—The Secretary shall not take into consideration any animal testing on a finished cosmetic product or an ingredient that occurs on or after the date of enactment of this subchapter with respect to any determination as to whether a cosmetic or ingredient meets the safety standard under section 614(a).

- **SEC. 624. Ban on Animal Testing**

"(c) EXCEPTION.—Subsections (a) and (b) shall not apply with respect to animal testing if—
"(1) the animal testing is for the purpose of determining whether an ingredient, or the relevant category of ingredients, meets the safety standard under section 614(a); and
"(2) the Secretary determines that the safety of the ingredient, or the relevant category of ingredients, cannot be established using a non-animal testing method that is validated by the Interagency Coordinating Committee on the Validation of Alternative Methods.

Humane Cosmetics Act H.R. 2790 115th Congress

- Cosmetic defined as in the FDCA – finished product and ingredients.
- COSMETIC ANIMAL TESTING.—The term "cosmetic animal testing" means the internal or external application or exposure of any cosmetic to the skin, eyes, or other body part of a live non-human vertebrate for purposes of evaluating the safety or efficacy of a cosmetic.
- Prohibits:
- (a) TESTING.—It shall be unlawful for any entity, whether private or governmental, to conduct or contract for cosmetic animal testing that occurs in the United States and is for the purpose of developing a cosmetic for sale in or affecting interstate or foreign commerce. Goes into effect on Date of enactment.
- (b) SALE OR TRANSPORT.—It shall be unlawful to sell, offer for sale, or knowingly transport in interstate commerce any cosmetic if the final product or any component thereof was developed or manufactured using cosmetic animal testing conducted or contracted for after the effective date (3 years after the date of enactment)

Penalties for violation of HR 2790

- (a) IN GENERAL.—In addition to any other penalties applicable under law, the Secretary of Health and Human Services shall assess whoever violates any provision of this Act a civil penalty of not more than $10,000 for each such violation.
- (b) MULTIPLE VIOLATIONS.—Each violation of this Act with respect to a separate animal, and each day that a violation of this Act continues, constitutes a separate offense.

A05145 State of New York Assembly 2017 - 2018

- Introduced by M. of A. L. ROSENTHAL, BARRETT, GOTTFRIED -- Multi-Sponsored by -- M. of A. GLICK -- read once and referred to the Committee on Economic Development
- Defines Cosmetics as defined in the FDCA (products plus components).
- Defines Cosmetic Animal Testing the internal or external application or exposure of any cosmetic to the skin, eyes, or other body part of a live non-human vertebrate for the purpose of evaluating the safety or efficacy of a cosmetic.

A05145 State of New York Assembly 2017 – 2018

- it shall be unlawful for any person, firm, partnership, corporation or association or agent or employee thereof to manufacture, knowingly import for profit, sell at retail or offer for sale at retail, any cosmetic if the final product or any component thereof was developed or manufactured using cosmetic animal testing after this section shall have become a law.
- Whenever the attorney general shall believe from evidence satisfactory to him or her that any person, firm, partnership, corporation or association or agent or employee thereof has violated any provision of this section, he or she may bring an action or special proceeding in the supreme court for a judgment enjoining the continuance of such violation and for a civil penalty of not more than five hundred dollars for the first violation and not more than one thousand dollars for each subsequent violation. This section shall only apply to cosmetic ingredients that were developed or manufactured predominately for cosmetics.

ASSEMBLY RESOLUTION No. 157
STATE OF NEW JERSEY 218th LEGISLATURE

- This resolution urges the President and Congress to enact the "Humane Cosmetics Act," currently introduced in Congress as H.R.2790, which would ban the testing of cosmetics on animals in the United States, and would also ban the sale of products that used animal testing after the effective date of the act.
- Every year, countless animals are poisoned and killed in tests that attempt to evaluate the hazards of consumer products and their ingredients. Despite the widespread availability of effective alternatives to animal testing, many cosmetics companies still conduct testing on animals. By both banning animal testing in the United States and prohibiting the sale of products that have been tested on animals, the enactment of this legislation would help reduce animal cosmetics testing worldwide, and bring the United States' cosmetics policy in line with more than 30 countries that have already implemented bans on animal testing and the sale of animal-tested cosmetics, including the European Union, Israel, Norway, Switzerland, and India.
- The Humane Cosmetics Act has been endorsed by 195 companies in the cosmetics industry, and is supported both by Republican and Democratic cosponsors. By enacting this legislation, the United States can show moral leadership without compromising product safety or business profitability.

ASSEMBLY, No. 4818
STATE OF NEW JERSEY 218th LEGISLATURE

- "Animal test" means the internal or external application of a cosmetic, or any ingredient thereof, to a body part of a live, nonhuman vertebrate.
- "Cosmetic" means any substance intended to be applied to or introduced into any part of the human body for the purposes of cleansing, promoting attractiveness, or altering the appearance, including, but not limited to, lipstick, make-up, deodorant, shampoo, and conditioner.
- "Ingredient" means any component of a cosmetic as defined by 21 C.F.R. 700.3.
- "Manufacturer" means any person whose name appears on the label of a cosmetic product pursuant to the requirements of 21 C.F.R. 701.12.
- "Supplier" means any entity that supplies, directly or through a third party, any ingredient used in the formulation of a manufacturer's cosmetic.

ASSEMBLY, No. 4818
STATE OF NEW JERSEY 218th LEGISLATURE

- No person or manufacturer shall sell or offer for sale in the State any cosmetic that was developed or manufactured using an animal test, if the test was conducted or contracted by the manufacturer or any supplier of the manufacturer on or after January 1, 2020.
- c. The prohibitions in subsection b. of this section do not apply to cosmetics developed or manufactured using an animal test if:
- (1) The animal test is required by a federal or State regulatory authority and:
- (a) the ingredient that requires an animal test is in wide use and cannot be replaced by another ingredient,
- (b) a specific human health problem is associated with the ingredient and the need to conduct an animal test on the ingredient is justified and supported by a research protocol, and
- (c) there is no non-animal test that is accepted by the relevant federal or State regulatory authority as a means to gather the relevant data;
- (2) The animal test is conducted to comply with a requirement of a foreign regulatory authority, if no evidence derived from the test is relied upon to substantiate the safety of the cosmetic pursuant to federal or State regulations; or

(3) The animal test is conducted on a product or ingredient subject to the requirements of chapter V of the federal "Food, Drug, and Cosmetic Act," 21 U.S.C. s.351 et seq.

ASSEMBLY, No. 4818
STATE OF NEW JERSEY 218th LEGISLATURE

- d. The prohibitions in subsection b. of this section do not apply to cosmetics that were sold in the State or tested on animals prior to January 1, 2020, even if the cosmetic is manufactured after that date.
- e. Any person or manufacturer that violates this section shall be subject to a penalty of up to $1,000 for each offense, to be collected in a civil action by a summary proceeding under the "Penalty Enforcement Law of 1999," P.L.1999, c.274 (C.2A:58-10 et seq.). If the violation is of a continuing nature, each day during which it continues constitutes an additional, separate, and distinct offense. The director of the Division of Consumer Affairs in the Department of Law and Public Safety may enforce the provisions of this section. Injunctive relieve is available for the Division of Consumer Affairs.

SB No. 2115 Banning Animal Testing in Hawaii

- Cosmetics; animal testing; prohibition. (a) Notwithstanding any other law to the contrary, it shall be unlawful for any cosmetic manufacturer to knowingly import for profit, sell at retail, or offer for sale at retail in this State, any cosmetic if the final product or any component thereof was developed or manufactured through use of animal testing that was performed on or after January 1, 2020.
- (b) This section shall only apply to ingredients used predominantly for cosmetics.
- Cosmetics means: 1) Articles intended to be rubbed, poured, sprinkled, or sprayed on, introduced into, or otherwise applied to the human body or any part thereof for cleansing, beautifying, promoting attractiveness, or altering the appearance, including but not limited to personal hygiene products such as deodorant, shampoo, or conditioner; or (2) Articles intended for use as a component of any such articles.

SB No. 2115 Banning Animal Testing in Hawaii

- c) Any violation of this section shall be punishable by a fine of not more than $500 for the first violation and a fine of not more than $1,000 for each subsequent violation.
- (d) Violations of this section shall be prosecuted by the attorney general or prosecutor of the county in which the violation occurred.
- (e) When prosecuting a violation of this section pursuant to subsection (d), the attorney general or prosecutor may review the testing data upon which a cosmetic manufacturer has relied in the development or manufacturing of any cosmetic product sold in the State.
- "Cosmetic manufacturer" means any individual, partnership, corporation, association, or other legal relationship that produces cosmetics that are sold or offered for sale in this State."

California law banning animal testing for Cosmetics

- 1834.9.5. (a) Notwithstanding any other law, it is unlawful for a manufacturer to import for profit, sell, or offer for sale in this state, any cosmetic, if the cosmetic was developed or manufactured using an animal test that was conducted or contracted by the manufacturer, or any supplier of the manufacturer, on or after January 1, 2020.
- (b) For purposes of this section, the following terms apply:
- (1) "Animal test" means the internal or external application of a cosmetic, either in its final form or any ingredient thereof, to the skin, eyes, or other body part of a live, nonhuman vertebrate.
- (2) "Cosmetic" means any article intended to be rubbed, poured, sprinkled, or sprayed on, introduced into, or otherwise applied to the human body or any part thereof for cleansing, beautifying, promoting attractiveness, or altering the appearance, including, but not limited to, personal hygiene products such as deodorant, shampoo, or conditioner.

California law banning animal testing for Cosmetics

- (3) "Ingredient" means any component of a cosmetic as defined by Section 700.3 of Title 21 of the Code of Federal Regulations.
- (4) "Manufacturer" means any person whose name appears on the label of a cosmetic product pursuant to the requirements of Section 701.12 of Title 21 of the Code of Federal Regulations.
- (5) "Supplier" means any entity that supplies, directly or through a third party, any ingredient used in the formulation of a manufacturer's cosmetic.

California law banning animal testing for Cosmetics

- (c) The prohibitions in subdivision (a) do not apply to the following:
- (1) An animal test of any cosmetic that is required by a federal or state regulatory authority if all of the following apply:
- (A) The ingredient is in wide use and cannot be replaced by another ingredient capable of performing a similar function.
- (B) A specific human health problem is substantiated and the need to conduct animal tests is justified and is supported by a detailed research protocol proposed as the basis for the evaluation.
- (C) There is not a nonanimal alternative method accepted for the relevant endpoint by the relevant federal or state regulatory authority.
- (2) An animal test that was conducted to comply with a requirement of a foreign regulatory authority, if no evidence derived from the test was relied upon to substantiate the safety of the cosmetic sold in California by the manufacturer.
- (3) An animal test that was conducted on any product or ingredient subject to the requirements of Chapter V of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 351 et seq.).
- (4) An animal test that was conducted for noncosmetic purposes in response to a requirement of a federal, state, or foreign regulatory authority, if no evidence derived from the test was relied upon to substantiate the safety of the cosmetic sold in California by the manufacturer. A manufacturer is not prohibited from reviewing, assessing, or retaining evidence from an animal test conducted pursuant to this paragraph.

California law banning animal testing for Cosmetics

- (d) A violation of this section shall be punishable by a fine of five thousand dollars ($5,000) and an additional one thousand dollars ($1,000) for each day the violation continues.
- (e) A violation of this section may be enforced by the district attorney of the county in which the violation occurred, or by the city attorney of the city in which the violation occurred. The civil fine shall be paid to the entity that is authorized to bring the action.
- (f) A district attorney or city attorney may, upon a determination that there is a reasonable likelihood of a violation of this section, review the testing data upon which a cosmetic manufacturer has relied in the development or manufacturing of the relevant cosmetic product sold in the state. Information provided under this section shall be protected as a trade secret as defined in subdivision (d) of Section 3426.1. Consistent with the procedures described in Section 3426.5, a district attorney or city attorney shall enter a protective order with a manufacturer before receipt of information from a manufacturer pursuant to this section, and shall take other appropriate measures necessary to preserve the confidentiality of information provided pursuant to this section.

California law banning animal testing for Cosmetics

- (g) This section shall not apply to either of the following:
- (1) A cosmetic, if the cosmetic, in its final form, was sold in California or tested on animals prior to January 1, 2020, even if the cosmetic is manufactured after that date.
- (2) An ingredient, if the ingredient was sold in California or tested on animals prior to January 1, 2020, even if the ingredient is manufactured after that date.

Comparison of the California Law to the Bill as Introduced

- Exemptions and limitations on the ban added through amendments supported by industry trade associations.
- Ban and liability applied only to animal testing conducted by the manufacturer or supplier of the product/ ingredient;
- Included exemptions for animal testing required by Federal or state regulatory authorities, or international regulatory authorities;
- animal testing required for drug testing;
- animal testing conducted for non cosmetic use required by law.

Thank you

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115TH CONGRESS
2D SESSION

H. R. 6903

To amend title VI of the Federal Food, Drug, and Cosmetic Act to ensure the safe use of cosmetics, and for other purposes.

IN THE HOUSE OF REPRESENTATIVES

SEPTEMBER 26, 2018

Ms. SCHAKOWSKY introduced the following bill; which was referred to the Committee on Energy and Commerce, and in addition to the Committee on Education and the Workforce, for a period to be subsequently determined by the Speaker, in each case for consideration of such provisions as fall within the jurisdiction of the committee concerned

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A BILL

To amend title VI of the Federal Food, Drug, and Cosmetic Act to ensure the safe use of cosmetics, and for other purposes.

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled,

SECTION 1. SHORT TITLE; TABLE OF CONTENTS.

(a) SHORT TITLE.—This Act may be cited as the ''Safe Cosmetics and Personal Care Products Act of 2018''.

(b) TABLE OF CONTENTS.—The table of contents of this Act is as follows:

SEC. 2. COSMETIC REGULATION.

(a) IN GENERAL.—Chapter VI of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 361 et seq.) is amended—

(1) by inserting before section 601 the following:

"Subchapter A—Adulterated and Misbranded Cosmetics";

and

(2) by adding at the end the following:

"Subchapter B—Regulation of Cosmetics

"SEC. 611. DEFINITIONS.

''In this subchapter:

''(1) BRAND OWNER.—The term 'brand owner' means the entity responsible for bringing a cosmetic to market.

''(2) CONTAMINANT.—The term 'contaminant' means unintended substances, such as those that can originate from sources outside the chemical pathway, chemical processes, storage of primary substances, instability of the packaging or harmful by-products of the manufacturing process.

''(3) DOMESTIC ESTABLISHMENT.—The term 'domestic establishment' means an establishment located in any State that brings a cosmetic to market.

''(4) FOREIGN ESTABLISHMENT.—The term 'foreign establishment' means an establishment that brings a cosmetic to market and exports those cosmetics to the United States.

''(5) INGREDIENT.—The term 'ingredient' means a chemical in a cosmetic, including—

''(A) chemicals that provide a technical or functional effect;

''(B) chemicals that have a technical or functional effect in the cosmetic, including the

components of intentionally added fragrance ingredients and colorants and intentional breakdown products of an added chemical that also have a functional or technical effect in the cosmetic;

"(C) processing aids that are present by reason of having been added to a cosmetic during the processing of such cosmetic;

"(D) substances that are present by reason of having been added to a cosmetic during processing for their technical or functional effect;

"(E) the components of a fragrance, flavor, or preservative; and

"(F) any individual component that the Secretary deems an ingredient for purposes of this chapter.

"(6) MANUFACTURER.—The term 'manufacturer' means the entity that produces ingredients or combines one or more ingredients to produce a cosmetic product.

"(7) MICROBUSINESS.—The term 'microbusiness' means a business—

"(A) that is a brand owner as defined in this subchapter; and

"(B) that has annual sales receipts for cosmetic products that do not exceed $2,000,000.

"(8) PROFESSIONAL USE.—The term 'professional use' means the use of any cosmetic—

"(A) by an employee (within the scope of the employment of such employee) of; or

"(B) purchased by a consumer in,

a hair salon, nail salon, beauty salon, spa, or other establishment that provides cosmetic treatment services for humans.

"(9) REASONABLE CERTAINTY OF NO HARM.—With respect to an ingredient or cosmetic, the term 'reasonable certainty of no harm' means that no harm will be caused to members of the general population or any vulnerable population by aggregate exposure to the cosmetic or ingredient, taking into account possible harmful effects from—

"(A) low-dose exposures to the cosmetic or ingredient;

"(B) additive effects resulting from repeated exposure to the cosmetic or ingredient over time; or

"(C) cumulative exposure resulting from all sources, including both the cosmetic or ingredient and environmental sources.

''(10) REPRODUCTIVE OR DEVELOPMENTAL TOXICITY.—With respect to an ingredient or cosmetic, the term 'reproductive or developmental toxicity' means that the ingredient or cosmetic can contribute to biologically adverse effects on the development of humans or animals, including effects on the female or male reproductive system, the endocrine system, fertility, pregnancy, pregnancy outcomes, or modifications in other functions of the body that are dependent on the integrity of the reproductive system as well normal fetal development.

''(11) SERIOUS ADVERSE EVENT.—The term 'serious adverse event' means—

''(A) an acute or chronic response that results in death, a life-threatening experience, short- or long-term hospitalization, a persistent or significant disability or incapacity, a congenital anomaly or birth defect, serious and persistent rashes or infections, significant hair loss, permanent or significant alteration of appearance, or impacts to maternal health, including placentia previa, gestational diabetes, and miscarriage;

''(B) an event that requires, based on a reasonable medical judgment, a medical or surgical intervention; or

''(C) any other serious adverse health-related event associated with the use of the product.

''(12) SUPPLIER.—The term 'supplier' means the entity that supplies ingredients, raw materials, or specific components of a cosmetic product, including packaging.

''(13) VULNERABLE POPULATIONS.—The term 'vulnerable populations' includes pregnant women, infants, children, the elderly, individuals with a compromised immune system, and highly exposed populations, including workers employed by a hair salon, nail salon, beauty salon, spa, or cosmetic manufacturing plant.

''SEC. 612. REGISTRATION OF ESTABLISHMENTS AND REGISTRATION FEES.

''(a) REGISTRATION.—

''(1) IN GENERAL.—Beginning 1 year after the date of the enactment of this subchapter, and annually thereafter, any brand owner (except for microbusinesses) engaged in bringing a cosmetic to market for use in the United States shall register with

the Secretary and pay to the Secretary the applicable fee, as established under the fee schedule in subsection (e).

''(2) RULES FOR DOMESTIC AND FOREIGN ESTABLISHMENTS.—To be registered under paragraph (1)—

''(A) as a domestic establishment, the owner, operator, or agent in charge of the domestic establishment shall submit a registration to the Secretary; or

''(B) as a foreign establishment, the owner, operator, or agent in charge of the foreign establishment shall—

''(i) submit a registration to the Secretary; and

''(ii) include with the registration the name of the United States agent for the foreign establishment.

''(3) NEW ESTABLISHMENTS.—Any brand owner that initially brings a cosmetic to market after the date on which the requirements of paragraph (1) apply shall, not later than 60 days after the date on which the establishment brings a cosmetic to market, register with the Secretary and pay the applicable fee, as required under paragraph (1).

''(b) SUBMISSION OF REGISTRATION.—

''(1) IN GENERAL.—In order to register under subsection (a), an establishment (referred to in this section as the 'registrant') shall submit to the Secretary, with respect to any cosmetics that the establishment brings to market, all of the following:

''(A) Any information necessary to notify the Secretary of the name, address, and legal status of each establishment at which, and all trade names under which, the registrant brings cosmetics to market.

''(B) A description of the establishment's activities with respect to cosmetics, including a list of all cosmetic products brought to market by the establishment and the functions of such cosmetics.

''(C) The gross receipts or sales for the establishment from cosmetics.

''(2) NOTIFICATION OF CHANGES.—When submitting the annual registration, the registrant shall notify the Secretary of changes to the information described in paragraph (1).

''(c) PROCEDURE.—Upon receipt of a completed registration submitted under subsection (a), the Secretary shall notify the registrant of the receipt of such registra-

tion and assign a registration number to each registered establishment.

''(d) LIST OF REGISTERED ESTABLISHMENTS.—

''(1) MAINTENANCE OF LIST.—The Secretary shall—

''(A) compile, maintain, and update as appropriate, a list of establishments that are registered under this section;

''(B) make such list publicly available, including by posting such list on the public Web site of the Food and Drug Administration;

''(C) remove from such list the name of any establishment that fails to register in accordance with this section; and

''(D) indicate on such list any establishment which has had its registration suspended or cancelled by the Secretary under this section.

''(2) APPLICATION OF FOIA.—

''(A) REGISTRATION DOCUMENTS.—Any registration documents submitted pursuant to this section shall not be subject to disclosure under section 552 of title 5, United States Code.

''(B) OTHER INFORMATION.—Information derived from—

''(i) the list under paragraph (1); or

''(ii) registration documents submitted pursuant to this section,

shall not be subject to disclosure under section 552 of title 5, United States Code, except to the extent that such information discloses the identity or location of a specific registrant.

''(e) FEE SCHEDULE.—A schedule of fees shall be developed by the Secretary to provide for oversight and enforcement of this subchapter. The fee structure shall—

''(1) be prorated based on the establishment's gross receipts or sales; and

''(2) only be assessed on companies with annual gross receipts or sales of cosmetics that exceed $10,000,000.

''(f) SUSPENSION AND CANCELLATION OF REGISTRATION.—

''(1) CRITERIA FOR SUSPENSION.—Registration under this section is subject to suspension if the Secretary finds—

''(A) the information submitted by the establishment for registration under subsection (a) is incomplete, inaccurate, or out of date;

''(B) the establishment fails to notify the Secretary of changes required under subsection (b)(2);

''(C) the establishment fails to pay registration fees, as required under subsection (a), in a timely manner; or

''(D) the establishment violates any portion of this chapter.

''(2) SUSPENSION OF REGISTRATION.—If the Secretary determines that an establishment is subject to suspension under this subsection and that it is appropriate to suspend the registration of such establishment, the Secretary shall—

''(A) suspend the registration of such establishment; and

''(B) provide a notice of suspension to such establishment.

''(3) CANCELLATION.—If the establishment fails to correct the issue that resulted in the suspension under paragraph (2) before the last day of the 30-day period beginning on the date that the establishment receives notice under such paragraph, the Secretary may cancel the registration of such establishment.

''(g) RECORDKEEPING.—All establishments that are required to register under this section shall maintain records that include a current list of suppliers and manufacturers, if the registrant does not manufacture or package its own product. Those records shall be accessible by the Secretary upon request for review or audit.

"SEC. 613. INGREDIENTS LABELS ON COSMETICS.

''(a) IN GENERAL.—Subject to subsections (b) and (c), the Secretary shall require that the label on each package of cosmetics (including cosmetics for retail sale and including cosmetics for professional use) bears a declaration of the name of each ingredient in such cosmetic in descending order of predominance.

''(b) ADJUSTMENTS FOR LABEL SIZE.—

''(1) RULES FOR SMALL PRODUCTS.—Not later than 6 months after the date of the enactment of this subchapter, the Secretary shall issue regulations that apply to any cosmetic for which the product packaging is not of sufficient size to bear or contain a label that meets the requirements of subsection (a).

''(2) REQUIREMENTS FOR PUBLIC DISCLOSURE.—Such regulations shall establish requirements for listing ingredients on the label of such

cosmetics and additional requirements for public disclosure of the ingredients in such cosmetics.

''(c) SPECIAL RULE FOR CONTAMINANTS.—The Secretary shall require, in the case of a contaminant, that a contaminant be declared on the label of a cosmetic, in the same manner as an ingredient under subsection (a), if the contaminant is present at the lower of the following levels:

''(1) A level that is greater than one part-per-billion by weight of product formation.

''(2) A level that is greater than one percent of the restriction on the concentration for such contaminant for such use, as determined by the Secretary under section 616(a)(2).

''(d) LABELING OF NANOMATERIALS IN COSMETICS.—The Secretary may require that—

''(1) minerals and other particulate ingredients be labeled as 'nano-scale' on a cosmetic ingredient label or list if not less than 1 percent of the ingredient particles in the cosmetic are 100 nanometers or smaller in not less than 1 dimension; and

''(2) other ingredients in a cosmetic be designated with scale-specific information on a cosmetic ingredient label or list if such ingredients possess scale-specific hazard properties.

''(e) LABELING OF INGREDIENTS IN COSMETICS SOLD THROUGH INTERNET COMMERCE.—The Secretary shall require—

''(1) in the case of a cosmetic sold on the Web site of an Internet vendor, that the brand owner of such cosmetic provide to such Internet vendor a list of the ingredients of the cosmetic; and

''(2) that each Internet vendor display the list of ingredients of a cosmetic sold by such vendor on the Web page that is the primary Web page providing information relating to the sale of such cosmetic on the Web site of the vendor.

''(f) TRADE SECRETS.—Notwithstanding any other provision of law, an ingredient required to be listed on a label under this section shall not be treated as a trade secret.

''(g) APPLICATION.—Beginning 18 months after the date of the enactment of this subchapter, the requirements of this section shall apply to—

''(1) all cosmetics that are available for retail sale (including such cosmetics for professional use); and

''(2) brand owners and Internet vendors of such cosmetics.

"SEC. 614. SAFETY STANDARD AND GOOD MANUFACTURING PRACTICES.

"(a) SAFETY STANDARD.—

"(1) IN GENERAL.—Taking into account the expected use of a cosmetic, the Secretary shall establish a safety standard that, with respect to a cosmetic or an ingredient in a cosmetic provides a reasonable certainty of no harm (as such term is defined in section 611(9)) from exposure to the cosmetic or ingredient and protects the public from any known or anticipated adverse health effects associated with the cosmetic or ingredient.

"(2) STANDARDS FOR ESTABLISHING SAFETY STANDARD.—In establishing the safety standard under paragraph (1), the Secretary shall ensure that—

"(A) the likely level of exposure to all sources of the ingredient or cosmetic (including environmental sources) that will result under the safety standard presents not more than a one in a million risk for any adverse health effect in any vulnerable population at the lower 95th percentile confidence interval; or

"(B) the safety standard results in exposure to the amount or concentration of an ingredient or cosmetic that is shown to produce

no adverse health effects, incorporating an margin of safety of at least 1,000 and considering the impact of cumulative exposure from all sources (including environmental sources).

''(3) USE OF OTHER FEDERAL STANDARDS.—If any Federal agency has promulgated a standard for an ingredient that satisfies the requirements under paragraph (1), the Secretary may treat such standard as the safety standard under paragraph (1) for purposes of such ingredient.

''(4) APPLICATION OF SAFETY STANDARD.—The Secretary may only determine that an ingredient or a cosmetic meets the safety standard under paragraph (1) if there is a reasonable certainty of no harm from exposure to the ingredient or cosmetic.

''(b) GOOD MANUFACTURING PRACTICES.—

''(1) IN GENERAL.—The Secretary shall issue guidance prescribing good manufacturing practices for cosmetics and ingredients, including quality control procedures that the Secretary determines are necessary, and shall update such regulations as necessary.

''(2) CONSIDERATION OF SMALL BUSINESS.—In developing the guidance under paragraph (1), the

Secretary shall consider how such practices will impact small businesses.

"SEC. 615. COSMETIC AND INGREDIENT SAFETY INFORMATION.

"(a) REQUIRED SUBMISSION OF ALL SAFETY INFORMATION.—

"(1) IN GENERAL.—Brand owners of cosmetics shall submit to the Secretary (in an electronic format that the Secretary shall determine) all data and information that the brand owner can access regarding the safety of the—

"(A) ingredients listed on the cosmetic label under section 613 for a cosmetic; and

"(B) cosmetic itself.

"(2) REQUIRED INFORMATION.—The required data and information under paragraph (1) shall include, for each ingredient in a cosmetic and for the cosmetic, the following:

"(A) Functions and uses.

"(B) Data and information on the physical, chemical, and toxicity of each such ingredient or cosmetic.

"(C) Exposure and fate information.

"(D) Results of all safety tests that the brand owner can access or has conducted.

''(E) Any other information used to substantiate the safety of such ingredient and cosmetic.

''(3) DEADLINES.—

''(A) INITIAL SUBMISSION.—A brand owner shall submit the data and information required under paragraph (1)—

''(i) in the case of an ingredient or cosmetic which is marketed for sale in interstate commerce on or before the date of the enactment of this subchapter, not later than 1 year after such date; and

''(ii) in the case of an ingredient or cosmetic which is not marketed for sale on or before such date—

''(I) not later than the end of the 14-month period beginning on the date of the enactment of this subchapter; or

''(II) if the ingredient or cosmetic is first marketed for sale in interstate commerce after the end of the period described in subclause (I), not later than 60 days after the date on which

such ingredient or cosmetic is first marketed for sale.

''(B) UPDATES.—

''(i) IN GENERAL.—Subject to clause (ii), a brand owner shall update the data and information submitted under subparagraph (A) annually.

''(ii) ADVERSE HEALTH EFFECTS.—In the case of information related to an adverse health effect that is suspected to be caused by an ingredient or a cosmetic, a brand owner shall update the information not later than 60 days after receiving such information.

''(4) SUPPLIER AND MANUFACTURER INFORMATION.—

''(A) USE OF SUPPLIER OR MANUFACTURER INFORMATION.—In order to meet the requirements of paragraph (1) with respect to an ingredient, a brand owner may submit safety data and information provided by the supplier or manufacturer of the ingredient or cosmetic.

''(B) SUPPLIER OR MANUFACTURER PROVISION OF INFORMATION.—If a brand owner requests that a supplier or manufacturer of an in-

gredient provide to such brand owner any of the data and information described under paragraph (2) or under section 617, such supplier or manufacturer shall provide such data and information to such brand owner not later than 90 days after receiving such request.

''(b) DATABASE.—

''(1) INITIAL PUBLICATION.—Not later than 1 year after the date of the enactment of this subchapter, the Secretary shall publish a comprehensive database that—

''(A) is publicly accessible, including on the public Web site of the Food and Drug Administration; and

''(B) contains all nonconfidential information (as such term is used under section 623) submitted under subsection (a)(1).

''(2) UPDATES.—Not later than 90 days after the Secretary receives new or updated information under subsection (a)(3)(B), the Secretary shall update the database under paragraph (1) with such information.

''(c) REVIEW AND EVALUATION OF INFORMATION.—

''(1) IN GENERAL.—Based on the data and information submitted under subsection (a)(1), avail-

able from an authoritative source (as such term is defined in paragraph (3), including data described under section 627(b)), and such other information as the Secretary may have available, the Secretary shall review and evaluate the safety of cosmetics and ingredients of cosmetics that are marketed in interstate commerce.

''(2) CONSIDERATION OF NANOMATERIALS.—The Secretary shall—

''(A) monitor developments in the scientific understanding from any adverse health effects related to the use of nanotechnology in the formulation of cosmetics (including progress in the standardization of testing methods and specific size definitions for nanomaterials); and

''(B) consider scale specific hazard properties of ingredients when reviewing and evaluating the safety of cosmetics and ingredients under paragraph (1).

''(3) AUTHORITATIVE SOURCE DEFINED.—For purposes of this paragraph, the term 'authoritative source' means—

''(A) the Environmental Protection Agency;

''(B) the International Agency for Research on Cancer;

''(C) the National Toxicity Program through the National Institutes of Health;

''(D) the California Environmental Protection Agency; and

''(E) any other authoritative international, Federal, and State entity, as determined by the Secretary.

"SEC. 616. LISTS OF INGREDIENTS AND REQUIRED RESPONSES.

''(a) PLACEMENT ON LIST.—

''(1) IN GENERAL.—Based on an initial review and evaluation of an ingredient under subsection (c), the Secretary shall place the ingredient on one of the following lists:

''(A) The prohibited and restricted list under subsection (b).

''(B) The safe without limits list under subsection (c).

''(C) The priority assessment list under subsection (d).

''(2) CONSIDERATIONS.—In determining the placement of an ingredient on a list under sub-

section (a), the Secretary shall consider whether the ingredient—

"(A) reacts with other substances to form harmful contaminants;

"(B) is found to be present in the body through biomonitoring;

"(C) is found in drinking water or air;

"(D) is a known or suspected neurological or immunological toxicant, respiratory asthmagen, carcinogen, teratogen, or endocrine disruptor, or have other toxicity concerns (including reproductive or developmental toxicity); or

"(E) is known to persist in the environment or bioaccumulate.

"(3) PRIORITIZATION OF INGREDIENTS THAT ARE FOOD.—In placing ingredients on the lists under paragraph (1), the Secretary shall prioritize the placement of ingredients that are food (as such term is defined under section 201(f)) on such lists.

"(b) PROHIBITED AND RESTRICTED LIST.—

"(1) IN GENERAL.—The Secretary shall issue, by regulation, a list of ingredients that are identified by the Secretary—

"(A) as prohibited for use because the Secretary determines that such ingredients are unsafe for use in cosmetics in any amount because such ingredients fail to meet the safety standard under section 614(a); or

"(B) as being subject to necessary restrictions in use or concentration to allow the use of the ingredient in a cosmetic to satisfy the safety standard.

"(2) INITIAL LIST.—

"(A) DEEMED PROHIBITED INGREDIENTS.—Effective as of the date of enactment of this subchapter, the following ingredients are deemed to be listed pursuant to paragraph (1)(A) as prohibited for use:

"(i) Benzophenones (benzophenone, benzophenone-1, benzophenone-3 aka oxybenzone).

"(ii) Octinoxate.

"(iii) Butylated Hydroxyanisole and Butylated Hydroxyoluen.

"(iv) Coal tar dyes (P-phenylenediamine).

"(v) Cocamide Diethanolamine.

''(vi) Dibutyalated Phthalate (Phthalates DBP), Bis(2-ethylhexyl) Phthalate (DEHP).

''(vii) Toluene.

''(viii) Styrene or Styrene acrylates.

''(ix) Formaldehydes (Methylene glycol/methanediol/formaldehyde) and Formaldehyde-releasing preservatives (DMDM hydantoin, diazolidinyl urea, imidazolidinyl urea, methenamine, quaternium-15, and sodium hydroxymethylglycinate).

''(x) Triclosan.

''(xi) Lead acetate or other lead compounds.

''(xii) Parabens (isoproylparaben, isobutylparaben, pheylparaben, benzylparaben, pentylparaben, propylparaben and butylparaben).

''(B) FIRST INGREDIENTS LISTED BY REGULATION.—Not later than 2 years after the date of enactment of this subchapter, the Secretary shall promulgate by final regulation the list required by subparagraphs (A) and (B) of paragraph (1), to supplement the ingredients

deemed by subparagraph (A) of this paragraph to be listed pursuant to paragraph (1)(A).

''(3) SPECIFICATION OF RESTRICTIONS.—In the case of any ingredient listed under paragraph (1)(B), the Secretary shall specify the restrictions on use or concentration that are necessary to satisfy the safety standard for such ingredient.

''(4) UPDATES.—After promulgating the initial list pursuant to paragraph (2)(B), the Secretary shall, at a minimum, annually update the list under paragraph (1), including any—

''(A) determinations under subsection (d)(3); or

''(B) new information that demonstrates that an ingredient fails to meet the safety standard, or requires restrictions on use to meet such standard.

''(5) MANUFACTURER REQUIREMENTS.—Not later than 1 year after the date that an ingredient is placed on a list under this subsection, any manufacturer using such ingredient in a cosmetic shall reformulate such cosmetic to—

''(A) eliminate the use of the ingredient, if it is listed under paragraph (1)(A); or

''(B) modify the use of the ingredient if it is listed under paragraph (1)(B), to meet the restrictions specified under paragraph (3).

''(c) SAFE WITHOUT LIMITS LIST.—

''(1) IN GENERAL.—Not later than 2 years after the date of the enactment of this subchapter, the Secretary shall issue, by regulation, a list of ingredients that the Secretary has determined are safe for use in cosmetics, without limits or restrictions.

''(2) STANDARD FOR INCLUSION IN LIST.—The Secretary may only include an ingredient on the list under paragraph (1) if the Secretary determines that the ingredient meets the safety standard under section 614(a), regardless of—

''(A) the type and form of cosmetic the ingredient is used in; and

''(B) the concentration of the ingredient that is used in a cosmetic.

''(3) UPDATES AND REDETERMINATIONS.—The Secretary shall annually update the list under paragraph (1) and may redetermine whether an ingredient distributed in commerce meets the safety standard if, in the judgment of the Secretary, new information raises a credible question as to whether the ingredient continues to meet the safety standard.

''(d) PRIORITY ASSESSMENT LIST AND RELATED SAFETY DETERMINATIONS.—

''(1) IN GENERAL.—Not later than 2 years after the date of the enactment of this subchapter, the Secretary shall develop and publish a priority assessment list of not less than 300 ingredients—

''(A) which, because of a lack of authoritative information on the safety of the ingredient, cannot be included on—

''(i) the list under subsection (b) (relating to prohibited and restricted ingredients); or

''(ii) the list under subsection (c) (relating to ingredients that are safe without limits); and

''(B) for which the Secretary has determined it is a priority to conduct a safety determination under paragraph (3).

''(2) ANNUAL ADDITION OF INGREDIENTS.—After the list is developed under paragraph (1), the Secretary shall annually add at least 100 additional ingredients to such list until all ingredients that are used in the formulation or manufacture of cosmetics have been added—

''(A) to such list;

''(B) to the list under subsection (b); or

''(C) to the list under subsection (c).

''(3) DETERMINATION OF WHETHER INGREDIENT MEETS SAFETY STANDARD.—

''(A) REVIEW OF PRIORITY INGREDIENTS.—During the 2-year period following the date on which an ingredient is placed on the list under paragraph (1), the Secretary shall—

''(i) collect data and information on such ingredient; and

''(ii) review and evaluate the safety of such ingredient.

''(B) DETERMINATION OF LIST PLACEMENT.—Not later than the end of the period under subparagraph (A), the Secretary shall issue a determination, based on the review and evaluation under such clause, that—

''(i) the ingredient meets the requirements for inclusion on a list under subsection (b) (relating to prohibited and restricted ingredients) or subsection (c) (relating to ingredients that are safe without limits); or

''(ii) insufficient information exists to place the ingredient on either such list.

"(C) GUIDANCE IN THE CASE OF INSUFFICIENT INFORMATION.—If the Secretary determines under subparagraph (B) that, with respect to an ingredient, insufficient information exists to place such ingredient on either of the lists under subsection (b) or subsection (c), the Secretary shall provide guidance on the data and information (including minimum data requirements and safety testing protocols) that the Secretary requires to evaluate whether the ingredient meets the safety standard under section 614(a) for purposes of placing such ingredient on such a list.

"(D) COMMENT PERIOD.—Upon issuing the determination under subparagraph (B), and, if applicable, the guidance under subparagraph (C), the Secretary shall provide a period of not less than 60 days for public comment on the determination before applying such determination to an ingredient, except that a shorter period for comment may be provided if the Secretary—

"(i) finds that it would be in the public interest to have a shorter period; and

"(ii) publicly declares the reasons for such finding.

"(4) RESPONSE TO INADEQUATE INFORMATION.—Not later than 18 months after the date that the Secretary issues guidance under paragraph (3)(C) with respect to an ingredient subject to a determination under paragraph (3)(B), a brand owner using such ingredient in a cosmetic shall—

"(A) reformulate such cosmetic to eliminate the use of the ingredient; or

"(B) provide the Secretary with the data and information specified in such guidance.

"(5) EVALUATION OF ADDITIONAL DATA AND INFORMATION.—With respect to an ingredient, not later than 6 months after the Secretary receives the data and information under paragraph (4)(B) the Secretary shall review such data and information and shall make a redetermination under paragraph (3)(B) for such ingredient, subject to the comment period under paragraph (3)(D).

"(6) LIMITATION.—If the Secretary has not placed an ingredient on either of the lists under subsection (b) and subsection (c) by the end of the 5-year period beginning on the date that such ingredient is first placed on the list under subsection (d),

beginning on the first day after such period such ingredient may not be—

''(A) used in a cosmetic; and

''(B) manufactured, imported, distributed, or marketed for use in cosmetics.

''SEC. 617. TREATMENT OF COSMETICS BASED ON INGREDIENT LISTS.

''(a) IN GENERAL.—Subject to subsections (b)(5) and (d)(4) of section 616, a brand owner may only distribute in interstate commerce a cosmetic that meets the safety standard under section 614(a).

''(b) PRESUMPTION RELATED TO THE SAFETY OF COSMETICS.—

''(1) IN GENERAL.—Subject to paragraph (2), for purposes of subsection (a), the Secretary shall presume that the following cosmetics meet the safety standard under section 614(a):

''(A) A cosmetic that is made solely of ingredients on the list under section 616(c)(1) (relating to ingredients that are safe without limits).

''(B) A cosmetic that is made solely of ingredients on the list under section 616(b)(1)(B) (relating to ingredients subject to restrictions) and the use of each of such ingredients in such

cosmetic is in compliance with the restrictions on the use of such ingredients specified under section 616(b)(3).

''(C) A cosmetic that is made solely of ingredients described under subparagraph (A) and subparagraph (B).

''(2) EXCEPTIONS.—The Secretary may require that a brand owner demonstrate that a cosmetic meets the safety standard under section 614(a) (including by requiring that the brand owner conduct safety testing, or request such safety testing from relevant suppliers and manufacturers, of a cosmetic described under paragraph (1)) if the cosmetic—

''(A) contains penetration enhancers, sensitizers, estrogenic chemicals, or other similar ingredients;

''(B) contains ingredients that react with each other or with other substances to form harmful byproducts; or

''(C) the Secretary has any additional reason to believe that such cosmetic does not meet the safety standard under section 614(a).

''(3) GUIDANCE.—If, under paragraph (2), the Secretary requires that a brand owner demonstrate that a cosmetic meets the safety standard under sec-

tion 614(a), the Secretary shall provide the brand owner with guidance on the data and information that the Secretary requires to evaluate whether the cosmetic meets the safety standard under such section.

''(c) NOTIFICATION OF FAILURE OF SECRETARY TO ACT.—If the Secretary fails to act by an applicable deadline under section 616 or this section, brand owners and manufacturers of an ingredient or a cosmetic affected by such failure of the Secretary to act shall issue to the Secretary, the public, and each known customer of the ingredient or cosmetic, a written notice that a determination by the Secretary of the safety of the ingredient for use in cosmetics is pending.

''SEC. 618. TREATMENT OF CONTAMINANTS.

''(a) PUBLICATION OF LIST.—Not later than 1 year after the date of the enactment of this subchapter, and annually thereafter, the Secretary shall publish a list of contaminants of concern linked to severe acute reactions or long-term adverse health effects, including—

''(1) ingredients used in cosmetics that may contain contaminants of concern;

''(2) combinations of ingredients that may create contaminants of concern when such ingredients interact;

''(3) contaminants of concern that may leech from product packaging into a cosmetic; and

''(4) any other contaminant of concern identified by the Secretary that are present in cosmetics.

''(b) EVALUATION; LABELING.—The Secretary shall use the process described in sections 615 and 616 to evaluate contaminants of concern for possible elimination or restriction in cosmetics. The Secretary shall require that a contaminant on the list under subsection (a) be declared on the label of a cosmetic, in the same manner as an ingredient under section 613.

''(c) REQUIREMENTS FOR TESTING.—

''(1) IN GENERAL.—Not later than 1 year after the date of enactment of this subchapter, the Secretary shall establish, by rule, requirements for testing ingredients and cosmetics for contaminants listed under subsection (a).

''(2) CONTENTS.—The requirements under paragraph (1) shall include—

''(A) testing methods and applicable protocols; and

''(B) maximum allowable detection limits for each contaminant in an ingredient or cosmetic.

''(3) UPDATE.—The Secretary shall annually update the requirements under paragraph (1).

''(d) SUPPLIER REQUIREMENTS.—Not later than 1 year after the promulgation of the rule under subsection (b)(1), a supplier of an ingredient that is used in a cosmetic shall, with respect to such ingredient—

''(1) comply with the requirements under subsection (b)(1) for any ingredient listed under subsection (a);

''(2) conduct similar testing on any ingredient that—

''(A) the supplier expects may be used in a cosmetic;

''(B) the supplier suspects may contain a contaminant of concern; and

''(C) is not listed under subsection (a); and

''(3) upon the sale of an ingredient to the manufacturer, provide to the manufacturer specifications for the ingredient that—

''(A) include the levels of contaminants present in such ingredient; and

''(B) are based on the results of the tests under paragraph (1) and paragraph (2).

''(e) BRAND OWNER REQUIREMENTS.—Not later than 1 year after the promulgation of the rule under sub-

section (b)(1), a brand owner of a cosmetic shall, with respect to each ingredient that the brand owner uses in a cosmetic—

''(1) obtain, from each supplier or manufacturer of the ingredient, specifications for the ingredient that include—

''(A) the level of each contaminant present in the ingredient; and

''(B) the detection limits of the analytical test used to detect the contaminant; or

''(2) comply with the requirements under paragraphs (1) and (2) of subsection (c) for the ingredient, in the same manner as if the brand owner were a supplier.

''SEC. 619. COSMETIC AND INGREDIENT STATEMENTS.

''(a) IN GENERAL.—Beginning 1 year after the date of the enactment of this subchapter, each brand owner of a cosmetic intended to be marketed in the United States shall submit electronically to the Secretary, for each cosmetic that is intended to be marketed in the United States, a statement containing—

''(1) the registration number of the brand owner;

''(2) the brand name and the product name for the cosmetic;

''(3) the applicable use for the cosmetic;

''(4) the ingredient list as it appears on the cosmetic label or insert, including the particle size range of any nanoscale cosmetic ingredients;

''(5) any warnings and directions for use from the cosmetic label or insert; and

''(6) the title and full contact information for the individual responsible for submitting and maintaining such statement.

''(b) NEW COSMETICS.—Any brand owner that begins to market a cosmetic after the date of the enactment of this subchapter shall comply with the requirements of subsection (a) beginning on the later of the following:

''(1) The end of the 18-month period beginning on the date of the enactment of this subchapter.

''(2) The 6-month period after the date on which the establishment begins to manufacture such cosmetic.

''(c) NOTIFICATION OF CHANGES.—The brand owner shall notify the Secretary annually of any change to the information required under subsection (a).

''(d) PROCEDURE.—Upon receipt of a completed statement described under subsection (a), the Secretary shall notify the brand owner of the receipt of such statement and assign a cosmetic statement number.

''(e) LIST.—The Secretary shall compile, maintain, and update as appropriate, a list of cosmetics for which statements are submitted under this section.

''(f) ACCESS TO SAFETY INFORMATION.—The cosmetic and ingredient statements collected under this section shall be added to the publicly accessible database created by the Secretary under section 615(b).

''SEC. 620. NOTIFICATION, NONDISTRIBUTION, AND RECALL OF ADULTERATED OR MISBRANDED COSMETICS.

''(a) NOTIFICATION OF ADULTERATED OR MISBRANDED COSMETICS.—

''(1) IN GENERAL.—A responsible party that has reason to believe that a cosmetic, when introduced into or while in interstate commerce, or while held for sale (regardless of whether such sale is the first sale of such cosmetic) after shipment in interstate commerce, is adulterated or misbranded in a manner that presents a reasonable probability that the use or exposure to the cosmetic (or an ingredient or component used in any such cosmetic) will cause a threat of serious adverse event shall notify the Secretary of the identity and location of the cosmetic.

''(2) MANNER OF NOTIFICATION.—Notification under paragraph (1) shall be made in such manner and by such means as the Secretary may require by regulation or guidance.

''(3) RESPONSIBLE PARTY DEFINED.—For purposes of this subsection, the term 'responsible party' means a brand owner, manufacturer, packager, retailer, or distributor of the cosmetic.

''(b) VOLUNTARY RECALL.—The Secretary may request that any person who distributes a cosmetic that the Secretary has reason to believe is adulterated, misbranded, or otherwise in violation of this Act voluntarily—

''(1) recall such cosmetic; and

''(2) provide for notice, including to individuals as appropriate, to persons who may be affected by the recall.

''(c) ORDER TO CEASE DISTRIBUTION.—

''(1) IN GENERAL.—If the Secretary has reason to believe that—

''(A) the use of, or exposure to, a cosmetic may cause serious adverse event;

''(B) the cosmetic is misbranded; or

''(C) the cosmetic is marketed, manufactured, packaged, or distributed by an unregistered brand owner;

the Secretary shall have the authority to issue an order requiring any person who distributes such cosmetic to immediately cease distribution of such cosmetic.

''(2) CEASE DISTRIBUTION AND NOTICE.—Any person who is subject to an order under paragraph (1) shall immediately cease distribution of such cosmetic and provide notification as required by such order.

''(3) APPEAL.—

''(A) 24 HOURS.—A person subject to an order under paragraph (1) may appeal such order to the Secretary within 24 hours of the issuance of such order.

''(B) CONTENTS OF APPEAL.—Such appeal may include a request for an informal hearing and a description of any efforts to recall such cosmetic undertaken voluntarily by the person, including after a request under subsection (b).

''(C) INFORMAL HEARING.—Except as provided in subsection (e), an informal hearing shall be held as soon as practicable, but not later than 5 calendar days (or less as determined by the Secretary) after such an appeal is

filed, unless the parties jointly agree to an extension.

''(D) IMPACT ON RECALL.—If an appeal is filed under subparagraph (A), the Secretary may not amend the order to require a recall under subsection (d) until after the conclusion of the hearing under subparagraph (C).

''(4) VACATION OF ORDER.—If the Secretary determines that inadequate grounds exist to support the actions required by the order under paragraph (1), the Secretary shall vacate the order.

''(d) ORDER TO RECALL.—

''(1) AMENDMENT.—Except as provided under subsection (e) and subject to subsection (c)(3)(D), if the Secretary determines that a recall of a cosmetic subject to an order under subsection (c) is appropriate, the Secretary shall amend the order to require a recall.

''(2) CONTENTS.—An amended order under paragraph (1) shall—

''(A) specify a timetable in which the recall will occur;

''(B) require periodic reports to the Secretary describing the progress of the recall; and

''(C) provide for notice, including to individuals as appropriate, to persons who may be affected by the recall.

In providing for such notice, the Secretary may allow for the assistance of health professionals, State or local officials, or other individuals designated by the Secretary.

''(3) NONDELEGATION.—An amended order under this subsection may only be issued by the Secretary or an official designated by the Secretary, and may not be delegated to another official or employee.

''(4) DETERMINATION.—If the Secretary determines that inadequate grounds exist to support the amendment made to the order under paragraph (1), the Secretary shall remove such amendment from such order.

''(e) EMERGENCY RECALL ORDER.—

''(1) IN GENERAL.—If the Secretary has credible evidence or information that a cosmetic subject to an order under subsection (c) presents an imminent threat of serious adverse event, the Secretary may issue an order requiring any person who distributes such cosmetic—

''(A) to immediately recall such cosmetic; and

''(B) to provide for notice, including to individuals as appropriate, to persons who may be affected by the recall.

''(2) RECALL AND NOTICE.—Any person who is subject to an emergency recall order under this subsection shall immediately recall such cosmetic and provide notification as required by such order.

''(3) APPEAL.—

''(A) 24 HOURS.—Any person subject to such an order may appeal such order to the Secretary within 24 hours of the issuance of such order.

''(B) CONTENTS OF APPEAL.—Such appeal may include a request for an informal hearing and a description of any efforts to recall such cosmetic undertaken voluntarily by the person, including after a request under subsection (b).

''(C) INFORMAL HEARING.—An informal hearing shall be held as soon as practicable after the appeal is filed under subparagraph (A), but not later than 5 calendar days after such an appeal is filed, or fewer days (as determined by the Secretary), unless the parties jointly agree to an extension.

''(4) VACATION OF ORDER.—If the Secretary determines that inadequate grounds exist to support the actions required by the order under paragraph (1), the Secretary shall vacate the order.

''(5) NONDELEGATION.—An order under this subsection may only be issued by the Secretary or an official designated by the Secretary, and may not be delegated to another official or employee.

''(f) NOTICE TO CONSUMERS AND HEALTH OFFICIALS.—The Secretary shall, as the Secretary determines to be necessary, provide notice of a recall order under this section to consumers to whom the cosmetic was, or may have been, distributed and to appropriate State and local health officials.

''(g) SUPPLY CHAIN INFORMATION.—

''(1) IN GENERAL.—In the case of a cosmetic that the Secretary has reason to believe is adulterated, misbranded, or otherwise in violation of this Act, the Secretary shall request that the brand owner named on the label of such cosmetic (as required under section 602(b)(1)) submit all of the following information:

''(A) The name and place of business of the manufacturer, packager, supplier, or distributor from which such entity received the

cosmetic or ingredients for manufacturing such cosmetic.

''(B) The name and place of business of any entity (including any retailer) that was provided with such cosmetic by the entity named on the label.

''(2) COLLECTION OF ADDITIONAL SUPPLY CHAIN INFORMATION.—In the case of a cosmetic that the Secretary has reason to believe is adulterated, misbranded, or otherwise in violation of this Act, to the extent necessary to protect the safety of the public, the Secretary may request that any entity (including a supplier of an ingredient, manufacturer, packer, distributor, or retailer) in the supply chain of such cosmetic submit to the Secretary information that is similar to the information described under subparagraphs (A) and (B) of paragraph (1).

''(3) MAINTENANCE OF RECORDS.—Any entity in supply chain of a cosmetic (including the brand owner named on the label of a cosmetic) shall—

''(A) maintain records sufficient to provide the information described in subparagraphs (A) and (B) of paragraph (1); and

''(B) provide such information to the Secretary upon the request of the Secretary.

''(h) SAVINGS CLAUSE.—Nothing contained in this section shall be construed as limiting the authority of the Secretary to issue an order to cease distribution of, or to recall, a cosmetic under any other provision of this Act.

''SEC. 621. PETITIONS.

''(a) IN GENERAL.—The Secretary shall complete and publish a review, and, if appropriate, immediately revise related, relevant information, including ingredient lists, ingredient restrictions or prohibitions, or ingredient or cosmetic safety determinations, not later than 6 months after the date on which the Secretary receives from any individual or entity a reasonable petition—

''(1) to prohibit or restrict an ingredient for use in cosmetics and list such ingredient on the list under section 616(b);

''(2) to remove an ingredient from the list of ingredients that are safe without limits under section 616(c);

''(3) to add an ingredient to the priority assessment list under section 616(d); or

''(4) to add an ingredient to the list of contaminants under section 618.

''(b) REASONABLE PETITION.—Not later than 1 year after the date of the enactment of this Act, the Secretary shall issue rules specifying the criteria which the Secretary

will use to determine if a petition submitted under this section is a reasonable petition.

"SEC. 622. MANDATORY REPORTING OF SERIOUS ADVERSE EVENTS.

"(a) SUBMISSION OF REPORT ON SERIOUS ADVERSE EVENTS.—The Secretary shall require that the brand owner of a cosmetic whose name appears on the label of a cosmetic marketed in the United States submit to the Secretary a report containing information received concerning any serious adverse event associated with the use of the cosmetic.

"(b) TIMING OF REPORT.—A report under subsection (a) shall be submitted to the Secretary not later than 15 business days after information concerning the serious adverse event is received at the place of business of the brand owner.

"(c) CONTENT OF REPORT.—A report under subsection (a) shall include the following information, to the extent to which the brand owner submitting the report has been able to verify the information:

"(1) The identity of the individual experiencing the adverse health event.

"(2) An identifiable report of such effect.

"(3) The name of the cosmetic suspected of causing such effect.

''(4) A description of the adverse health event.

''(d) PUBLIC AVAILABILITY AND PRIVACY.—

''(1) PUBLIC AVAILABILITY.—Subject to paragraph (2), the serious adverse event reports collected by the Secretary under this section shall be submitted electronically and shall be made accessible to the public.

''(2) PRIVACY.—

''(A) PERSONALLY IDENTIFIABLE INFORMATION.—Notwithstanding any other provision of law, personally identifiable information in serious adverse event reports provided to the Secretary under this section, shall not—

''(i) be made publicly available pursuant to any State or other law requiring disclosure of information or records; or

''(ii) otherwise be disclosed or distributed to any party without the written consent of the Secretary and the person submitting such information to the Secretary.

''(B) TREATMENT OF INFORMATION UNDER PRIVACY ACT AND FOIA.—A report submitted to the Secretary under this section, shall be considered to be a record about an individual under section 552a of title 5, United States

Code (commonly referred to as the ''Privacy Act of 1974'') and a medical or similar file the disclosure of which would constitute a violation of section 552 of such title 5 (commonly referred to as the ''Freedom of Information Act''), and shall not be publicly disclosed unless all personally identifiable information is redacted.

''SEC. 623. NONCONFIDENTIAL INFORMATION.

''(a) INFORMATION AVAILABLE TO PUBLIC.—Subject to subsection (c) and section 622(d)(2), all nonconfidential information submitted pursuant to this subchapter shall be made available to the public, including the following types of information:

''(1) The name, identity, and structure of a chemical substance, contaminant, or impurity that is an ingredient.

''(2) All information concerning function, exposure, toxicity data, health hazards, and environmental hazards for a cosmetic.

''(3) The functions of ingredients in cosmetics.

''(4) Fragrance, flavor, and colorants in a cosmetic.

''(b) CONFIDENTIAL INFORMATION.—The concentration of cosmetic ingredients used in a finished cosmetic

shall be considered confidential business information and may not be made available to the public under subsection (a).

''(c) PETITION FOR INFORMATION TO REMAIN CONFIDENTIAL.—

''(1) IN GENERAL.—The Secretary shall create a process for an entity to petition for nonconfidential information described in subsection (a) to remain confidential if the entity shows that there would be a serious negative impact to the entity's commercial interests if such information were disclosed to the public.

''(2) LIMITATION.—The Secretary may not approve a petition under paragraph (1) to the extent that such petition would prevent the public disclosure of—

''(A) the name, identity, and structure of any chemical substance, contaminant, or impurity that is an ingredient;

''(B) all health and safety data related to that substance, contaminant, or impurity; or

''(C) any data used to substantiate the safety of that substance, contaminant, or impurity.

"SEC. 624. BAN ON USE OF ANIMAL TESTING.

''(a) BAN.—Beginning on the date of enactment of this subchapter, it shall be unlawful for any entity to conduct, directly or pursuant to contract, animal testing for the purpose of developing a cosmetic for sale in or affecting interstate commerce.

''(b) LIMITATION ON CONSIDERATION OF DATA.—The Secretary shall not take into consideration any animal testing on a finished cosmetic product or an ingredient that occurs on or after the date of enactment of this subchapter with respect to any determination as to whether a cosmetic or ingredient meets the safety standard under section 614(a).

''(c) EXCEPTION.—Subsections (a) and (b) shall not apply with respect to animal testing if—

''(1) the animal testing is for the purpose of determining whether an ingredient, or the relevant category of ingredients, meets the safety standard under section 614(a); and

''(2) the Secretary determines that the safety of the ingredient, or the relevant category of ingredients, cannot be established using a non-animal testing method that is validated by the Interagency Coordinating Committee on the Validation of Alternative Methods.

''(d) VALIDATED, ELIGIBLE NON-ANIMAL TESTING METHODS.—

''(1) LIST.—The Secretary shall develop, maintain, and make publicly available a list of non-animal testing methods that—

''(A) are validated by the Interagency Coordinating Committee on the Validation of Alternative Methods; and

''(B) are eligible for use pursuant to the exception described in subsection (c).

''(2) INITIAL LIST; UPDATES.—The Secretary shall—

''(A) not later than 1 year after the date of enactment of this subchapter, publish the initial list under paragraph (1); and

''(B) annually thereafter, update such list.

''(e) GRANTS.—The Secretary shall award grants for the development of testing methods that may be used to replace animal testing pursuant to the exception described in subsection (c).

''SEC. 625. PRODUCT TESTING AND REVIEW AUDIT.

''The Secretary shall conduct annual audits of random samples of cosmetics to assess or test for acute negative reactions, pathogen hazards, contaminants, leaching

of packaging additives, mislabeling, or other relevant issues of concern (as determined by the Secretary).

"SEC. 626. RESOURCES FOR SMALL BUSINESSES.

"The Secretary shall provide technical support to assist small businesses in carrying out the requirements of this subchapter.

"SEC. 627. INTERAGENCY COOPERATION.

"(a) INTERAGENCY COUNCIL ON COSMETIC SAFETY.—There is established an Interagency Council on Cosmetic Safety for the purpose of sharing data and promoting collaboration on cosmetic safety between the Food and Drug Administration, the National Institute of Environmental Health Sciences, the Centers for Disease Control and Prevention, the Occupational Safety and Health Administration, and the Environmental Protection Agency.

"(b) USE OF DATA FROM FEDERAL SOURCES.—For purposes of this subchapter, the Secretary, as appropriate, shall request and utilize ingredient and cosmetic toxicity, use, and exposure data from other Federal agencies.

"SEC. 628. SAVINGS CLAUSE.

"Nothing in this Act affects the right of a State or a political subdivision of a State to adopt or enforce any regulation, requirement, or standard of performance that is different from, or in addition to, a regulation, require-

ment, liability, or standard for performance established pursuant to this Act unless compliance with both this Act and the State or political subdivision of a State regulation, requirement, or standard of performance is impossible, in which case the applicable provisions of this Act shall control.

"SEC. 629. AUTHORIZATION OF APPROPRIATIONS.

''There are authorized to be appropriated such sums as may be necessary to carry out this subchapter for each of the fiscal years 2014 through 2018.''.

(b) ADULTERATED AND MISBRANDED COSMETICS.—

(1) ADULTERATED COSMETICS.—Section 601 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 361) is amended in paragraph (a)—

(A) by striking '', except that this provision shall not apply to coal-tar hair dye'' and all that follows through ''or eyebrow dyes''; and

(B) by adding at the end the following:

''(f) If it is manufactured in a manner that fails to comply with section 617(a).

''(g) If it is imported, distributed, or marketed and—

''(1) it contains an ingredient on the list under section 616(b)(1)(A), and the manufacturer has not complied with section 616(b)(5)

with respect to such ingredient and such cosmetic; or

"(2) it contains an ingredient on the list under section 616(b)(1)(B), such ingredient is being used in a manner that violates the limit on use or concentration of such ingredient under section 616(b)(3), and the manufacturer has not complied with section 616(b)(5) with respect to such ingredient and such cosmetic.

"(h) If it is marketed by a brand owner that, with respect to such cosmetic, is required to demonstrate, under section 617(b)(2), that the cosmetic meets the safety standard and the brand owner has not yet submitted the required data under section 617(b)(3).".

(2) MISBRANDED COSMETICS.—Section 602 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 362) is amended—

(A) in paragraph (a), by inserting "or fails to meet the requirements of section 613 or 618(b)" before the period; and

(B) by adding at the end the following:

"(g) If it—

"(1) was brought to market by a brand owner that failed to register and pay the applicable fee as required under section 612;

"(2) is brought to market, manufactured, packaged, distributed, or sold in retail by a brand owner, manufacturer, packager, distributor, or retailer, respectively, who fails to notify the Secretary as required under section 620(a)(1);

"(3) is distributed in violation of an order under section 620(c);

"(4) is not recalled as required by an order under subsection (d) or (e) of section 620;

"(5) is manufactured in a manner that fails to comply with good manufacturing practices prescribed by the Secretary under section 614(b); or

"(6) is brought to market by a brand owner who fails—

"(A) to submit the statement required under section 619; or

"(B) notify the Secretary of changes to information contained in such report, as required by such section.".

(3) ADDITIONAL PROHIBITIONS.—Section 301 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 331) is amended—

(A) in paragraph (e), by inserting ''612,'' after ''564,'' each place it appears; and

(B) by adding at the end the following:

''(ccc) The failure of a brand owner, manufacturer, or supplier of a cosmetic or an ingredient for use in a cosmetic to submit and update data and information as required under section 615(a).

''(ddd) The manufacture, importation, distribution, or marketing of an ingredient for use in a cosmetic that is on the list under section 616(b)(1)(A).

''(eee) The failure of a supplier of an ingredient for use in a cosmetic—

''(1) to provide data and information as required by section 615(a)(4)(B); or

''(2) comply with the testing requirements under section 618(c).

''(fff) The failure of a manufacturer to comply with the requirements of section 618(d).

''(ggg) The failure of a brand owner of a cosmetic to comply with the requirement of reporting serious adverse events under section 622.

''(hhh) The conduct of animal testing in violation of section 624.''.

SEC. 3. WORKER ISSUES.

(a) IN GENERAL.—The Secretary of Labor shall promulgate an occupational safety and health standard under section 6 of the Occupational Safety and Health Act of 1970 (29 U.S.C. 655) that requires the following:

(1) MANUFACTURERS AND IMPORTERS.—Each manufacturer or importer selling any cosmetic for professional use shall—

(A) obtain or develop a material safety data sheet described in subsection (b) for each such cosmetic or personal care product that—

(i) the manufacturer or importer produces or imports; and

(ii) includes a hazardous chemical, or a product ingredient associated with any chemical hazard, that is classified as a health hazard in accordance with the criteria found in section 1910.1200(d) of title 29 of the Code of Federal Regulations, and any successor regulations; and

(B) make the material safety data sheet available on the manufacturer or importer's Web site (in addition to any other required

manner of making such sheet available) to distributors and employers, including salon owners, in English, Spanish, Vietnamese, and, upon request, other languages.

(2) DISTRIBUTORS.—Each distributor of a cosmetic or personal care product for professional use shall distribute and provide material safety data sheets described in subsection (b) in the same manner as a distributor of a chemical hazard is required to distribute and provide material safety data sheets under section 1910.1200(g) of title 29, Code of Federal Regulations, or any successor regulations.

(3) EMPLOYERS.—Each employer, including any operator of a salon, shall—

(A) have a material safety data sheet in the workplace for each cosmetic or personal care product for professional use that is used in the course of the employer's business;

(B) make such material safety data sheet available to all employees of the employer who are exposed or use the product to the same extent and in the same manner as material safety data sheets are required to be made available under section 1910.1200(g) of title 29, Code of

Federal Regulations, or any successor regulations; and

(C) upon request, provide employees with translations of such material safety data sheet in other languages, including Spanish and Vietnamese.

(b) CONTENTS OF MATERIAL SAFETY DATA SHEET.—A material safety data sheet for a cosmetic or personal care product for professional use described in this section shall—

(1) contain the information required in a material safety data sheet under section 1910.1200(g) of title 29, Code of Federal Regulations, or any successor regulations, for each hazardous chemical, or product ingredient associated with any chemical hazard, described in subsection (a)(1)(A)(ii); and

(2) include the following statement: ''This material safety data sheet is also available in multiple languages by contacting the manufacturer, using the contact information provided on this sheet.''.

(c) PROFESSIONAL USE DEFINED.—In this section, the term ''professional use'' has the meaning given such term in section 611(8) of the Federal Food, Drug, and Cosmetic Act except to the extent that such term applies

to a product that is sold as a retail product in any of the establishments listed under such definition.

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115TH CONGRESS
1ST SESSION

H. R. 2790

To phase out cosmetic animal testing and the sale of cosmetics tested on animals, and for other purposes.

IN THE HOUSE OF REPRESENTATIVES

JUNE 6, 2017

Ms. MCSALLY (for herself, Mr. BEYER, Mr. ROYCE of California, Mr. CÁRDENAS, Mr. LOBIONDO, Mr. TONKO, Mr. RODNEY DAVIS of Illinois, Mr. HUFFMAN, Mr. DONOVAN, Ms. TITUS, Mr. CURBELO of Florida, Ms. SLAUGHTER, Mr. MACARTHUR, Mr. HASTINGS, Ms. STEFANIK, Ms. SPEIER, Mr. YODER, Mr. GAETZ, Mr. KATKO, and Mr. DEUTCH) introduced the following bill; which was referred to the Committee on Energy and Commerce

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A BILL

To phase out cosmetic animal testing and the sale of cosmetics tested on animals, and for other purposes.

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled,

SECTION 1. SHORT TITLE.

This Act may be referred to as the ''Humane Cosmetics Act''.

SEC. 2. DEFINITIONS.

For purposes of this Act:

(1) COSMETIC.—The term ''cosmetic'' has the meaning given such term in section 201 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321).

(2) COSMETIC ANIMAL TESTING.—The term ''cosmetic animal testing'' means the internal or external application or exposure of any cosmetic to the skin, eyes, or other body part of a live non-human vertebrate for purposes of evaluating the safety or efficacy of a cosmetic.

SEC. 3. PROHIBITIONS.

(a) TESTING.—It shall be unlawful for any entity, whether private or governmental, to conduct or contract for cosmetic animal testing that occurs in the United States and is for the purpose of developing a cosmetic for sale in or affecting interstate or foreign commerce.

(b) SALE OR TRANSPORT.—It shall be unlawful to sell, offer for sale, or knowingly transport in interstate commerce any cosmetic if the final product or any component thereof was developed or manufactured using cosmetic animal testing conducted or contracted for after the effective date specified in section 5(a).

SEC. 4. CIVIL PENALTIES.

(a) IN GENERAL.—In addition to any other penalties applicable under law, the Secretary of Health and Human Services shall assess whoever violates any provision of this

Act a civil penalty of not more than $10,000 for each such violation.

(b) MULTIPLE VIOLATIONS.—Each violation of this Act with respect to a separate animal, and each day that a violation of this Act continues, constitutes a separate offense.

SEC. 5. EFFECTIVE DATES.

(a) PROHIBITION ON COSMETIC ANIMAL TESTING.—The prohibition specified in section 3(a) takes effect on the date that is 1 year after the date of enactment of this Act.

(b) PROHIBITION ON SALE.—The prohibition specified in section 3(b) takes effect on the date that is 3 years after the date of enactment of this Act.

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A05145 Text:

STATE OF NEW YORK

5145--A

2017-2018 Regular Sessions

IN ASSEMBLY

February 6, 2017

Introduced by M. of A. L. ROSENTHAL, BARRETT, GOTTFRIED -- Multi-Sponsored by -- M. of A. GLICK -- read once and referred to the Committee on Economic Development -- committee discharged, bill amended, ordered reprinted as amended and recommitted to said committee

AN ACT to amend the general business law, in relation to prohibiting the sale of cosmetics tested on animals

The People of the State of New York, represented in Senate and Assembly, do enact as follows:

Section 1. The general business law is amended by adding a new section 399-aaaa to read as follows:

§ 399-aaaa. Selling of animal tested cosmetics. 1. For the purposes of this section the following terms shall have the following meanings:

(a) "Cosmetic" shall mean (1) articles intended to be rubbed, poured, sprinkled, or sprayed on, introduced into, or otherwise applied to the human body or any part thereof for cleansing, beautifying, promoting attractiveness, or altering the appearance, including but not limited to personal hygiene products such as deodorant, shampoo or conditioner, and (2) articles intended for use as a component of any such articles.

(b) "Cosmetic animal testing" shall mean the internal or external

application or exposure of any cosmetic to the skin, eyes, or other body part of a live non-human vertebrate for the purpose of evaluating the safety or efficacy of a cosmetic.

2. It shall be unlawful for any person, firm, partnership, corporation or association or agent or employee thereof to manufacture, knowingly import for profit, sell at retail or offer for sale at retail, any cosmetic if the final product or any component thereof was developed or manufactured using cosmetic animal testing after this section shall have become a law.

3. Whenever the attorney general shall believe from evidence satisfactory to him or her that any person, firm, partnership, corporation or association or agent or employee thereof has violated any provision of

EXPLANATION--Matter in *italics* (underscored) is new; matter in brackets
[-] is old law to be omitted.

LBD05129-02-7

this section, he or she may bring an action or special proceeding in the supreme court for a judgment enjoining the continuance of such violation and for a civil penalty of not more than five hundred dollars for the first violation and not more than one thousand dollars for each subsequent violation. This section shall only apply to cosmetic ingredients that were developed or manufactured predominately for cosmetics.

§ 2. This act shall take effect on the three hundred sixty-fifth day after it shall have become a law.

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ASSEMBLY RESOLUTION No. 157
STATE OF NEW JERSEY
218th LEGISLATURE

INTRODUCED MAY 7, 2018

Sponsored by:
Assemblywoman CAROL A. MURPHY
District 7 (Burlington)

SYNOPSIS
Urges President and Congress to enact “Humane Cosmetics Act.”

CURRENT VERSION OF TEXT
As introduced.

An Assembly Resolution urging the President and Congress of the United States to enact the “Humane Cosmetics Act” concerning cosmetics testing on animals.

Whereas, Every year, countless animals are injured and killed in tests that attempt to evaluate the hazards of consumer products and their ingredients; and
Whereas, In an effort to measure toxicity, rats, mice, guinea pigs, rabbits, and other animals are forced to swallow or inhale massive quantities of test substances or have a chemical spread in their eyes or on their skin; and
Whereas, Tests on animals often do not predict outcomes in humans, and many non-animal test methods are available and continue to be developed; and
Whereas, Acute toxicity testing, eye and skin irritation testing, skin sensitization testing, carcinogenicity testing, and reproductive and developmental toxicity testing cause great pain to animals without necessarily providing more accurate conclusions about the safety of consumer products than non-animal testing alternatives; and
Whereas, The United States Food and Drug Administration advises cosmetics manufacturers to employ whatever testing is appropriate and effective for substantiating the safety of their products while noting that the federal Food, Drug, and Cosmetic Act does not specifically require the use of animals in testing cosmetics for safety; and
Whereas, The United States Consumer Product Safety Commission’s animal testing policy states that neither the Federal Hazardous Substances Act nor the commission’s regulations require animal testing and only require that a product be labeled to reflect the hazards associated with that product; and
Whereas, While some countries, such as China, require specific animal tests for these products, the European Union, Israel, and India have banned the sale of any cosmetics or cosmetics ingredients that have been tested on animals; and

Whereas, The “Humane Cosmetics Act,” introduced on June 6, 2017 as H.R.2790, would ban testing any cosmetics on animals, and would also ban the sale of any product that uses animal testing after the effective date of the act; and
Whereas, By both banning animal testing in the United States and prohibiting the sale of products that have been tested on animals, the “Humane Cosmetics Act” would help reduce animal cosmetics testing worldwide; and
Whereas, The congressional sponsors of the “Humane Cosmetics Act” have stated that the cosmetics industry already has safer, more cost-effective methods of testing that do not harm animals and American companies face no economic risk from this legislation; and
Whereas, The cosmetics industry is already using alternative cutting-edge testing methods that are safer and cheaper and which do not hurt animals, and the United States should show moral leadership by standing against the inhumane treatment of animals; and
Whereas, The “Humane Cosmetics Act” would bring the United States’ cosmetics policy in line with more than 30 countries that have already implemented bans on animal testing and the sale of animal-tested cosmetics, including the European Union, Israel, Norway, Switzerland, and India; and
Whereas, Of the 13 biggest importers of American cosmetics, eight countries have bans in place or legislation under consideration regarding animal testing, and American cosmetics companies already have to comply with these animal testing bans; and
Whereas, Seven hundred cosmetics brands in North America do not test products or ingredients on animals, and instead use other affordable, proven methods of testing and innovate with thousands of ingredients already proven safe for use; and
Whereas, The “Humane Cosmetics Act” has been endorsed by 195 companies in the cosmetics industry, and is supported by both Republican and Democratic cosponsors; now, therefore,

Be It Resolved by the General Assembly of the State of New Jersey:

1. This House urges the President and Congress of the United States to enact legislation (currently H.R.2790 of 2017), known as the “Humane Cosmetics Act,” to ban the testing of cosmetics on animals and also ban the sale of any cosmetics product that uses animal testing after the effective date of the act.

2. Copies of this resolution, as filed with the Secretary of State, shall be transmitted by the Clerk of the General Assembly to the President of the United States, the Majority and Minority Leaders of the United States Senate, the Speaker and Minority Leader of the United States House of Representatives, the Chair of the House of Representatives Committee on Energy and Commerce, and every member of the congressional delegation from the State of New Jersey.

STATEMENT

This resolution urges the President and Congress to enact the “Humane Cosmetics Act,” currently introduced in Congress as H.R.2790, which would ban the testing of cosmetics on animals in the United States, and would also ban the sale of products that used animal testing after the effective date of the act.

Every year, countles animals are poisoned and killed in tests that attempt to evaluate the hazards of consumer products and their ingredients. Despite the widespread availability of effective alternatives to animal testing, many cosmetics companies still conduct testing on animals. By both banning animal testing in the United States and prohibiting the sale of products that have been tested on animals, the enactment of this legislation would help reduce

animal cosmetics testing worldwide, and bring the United States' cosmetics policy in line with more than 30 countries that have already implemented bans on animal testing and the sale of animal-tested cosmetics, including the European Union, Israel, Norway, Switzerland, and India.

The Humane Cosmetics Act has been endorsed by 195 companies in the cosmetics industry, and is supported both by Republican and Democratic cosponsors. By enacting this legislation, the United States can show moral leadership without compromising product safety or business profitability.

ASSEMBLY, No. 4818

STATE OF NEW JERSEY

218th LEGISLATURE

INTRODUCED DECEMBER 17, 2018

Sponsored by:
Assemblyman ANTHONY S. VERRELLI
District 15 (Hunterdon and Mercer)

SYNOPSIS

Prohibits sale of cosmetic products that have been tested on animals.

CURRENT VERSION OF TEXT

As introduced.

AN ACT concerning cosmetic products that have been tested on animals and supplementing Title 4 of the Revised Statutes.

BE IT ENACTED *by the Senate and General Assembly of the State of New Jersey:*

1. a. For the purposes of this section:

"Animal test" means the internal or external application of a cosmetic, or any ingredient thereof, to a body part of a live, nonhuman vertebrate.

"Cosmetic" means any substance intended to be applied to or introduced into any part of the human body for the purposes of cleansing, promoting attractiveness, or altering the appearance, including, but not limited to, lipstick, make-up, deodorant, shampoo, and conditioner.

"Ingredient" means any component of a cosmetic as defined by 21 C.F.R. 700.3.

"Manufacturer" means any person whose name appears on the label of a cosmetic product pursuant to the requirements of 21 C.F.R. 701.12.

"Supplier" means any entity that supplies, directly or through a third party, any ingredient used in the formulation of a manufacturer's cosmetic.

b. No person or manufacturer shall sell or offer for sale in the State any cosmetic that was developed or manufactured using an animal test, if the test was conducted or contracted by the manufacturer or any supplier of the manufacturer on or after January 1, 2020.

c. The prohibitions in subsection b. of this section do not apply to cosmetics developed or manufactured using an animal test if:

(1) The animal test is required by a federal or State regulatory authority and:

(a) the ingredient that requires an animal test is in wide use and cannot be replaced by another ingredient,

(b) a specific human health problem is associated with the ingredient and the need to conduct an animal test on the ingredient is justified and supported by a research protocol, and

(c) there is no non-animal test that is accepted by the relevant federal or State regulatory authority as a means to gather the relevant data;

(2) The animal test is conducted to comply with a requirement of a foreign regulatory authority, if no evidence derived from the test is relied upon to substantiate the safety of the cosmetic pursuant to federal or State regulations; or

(3) The animal test is conducted on a product or ingredient subject to the requirements of chapter V of the federal "Food, Drug, and Cosmetic Act," 21 U.S.C. s.351 et seq.

d. The prohibitions in subsection b. of this section do not apply to cosmetics that were sold in the State or tested on animals prior to January 1, 2020, even if the cosmetic is manufactured after that date.

e. Any person or manufacturer that violates this section shall be subject to a penalty of up to $1,000 for each offense, to be collected in a civil action by a summary proceeding under the "Penalty Enforcement Law of 1999," P.L.1999, c.274 (C.2A:58-10 et seq.). If the violation is of a continuing nature, each day during which it continues constitutes an additional, separate, and distinct offense. The director of the Division of Consumer Affairs in the Department of Law and Public Safety may enforce the provisions of this section. The Superior Court and the municipal court shall have jurisdiction to enforce the provisions of the "Penalty Enforcement Law of 1999."

f. The Division of Consumer Affairs may institute a civil action for injunctive relief to enforce this act and to prohibit and prevent a violation of this act, and the court may proceed in the action in a summary manner.

2. This act shall take effect immediately.

STATEMENT

This bill would prohibit the sale or offer for sale of cosmetics that were developed or manufactured using animal tests on or after January 1, 2020.

Current law prohibits performing animal tests on products in New Jersey when there is an appropriate validated alternative test method. This bill would strengthen this prohibition with respect to cosmetics products, barring the sale of all cosmetics that were tested on animals, even if those tests were performed outside the State. Animal tests for cosmetics are frequently painful and harmful to the animal. Furthermore, alternative testing methods, such as the use of engineered human tissue and the use of computer models, are often cheaper and more accurate than animal testing, in addition to being cruelty-free.

The bill would not apply to cosmetics that were sold in the State or tested on animals before January 1, 2020. In addition, the bill would not apply to cosmetics that are required by a federal or State regulatory agency to be tested on animals, provided that certain conditions apply. The bill would also not apply to cosmetics that are required by a foreign regulatory agency to be tested on animals, as long as the safety of such cosmetics is independently verified using non-animal tests.

Violations of the provisions of the bill are punishable by fines of up to $1,000. The director of the Division of Consumer Affairs in the Department of Law and Public Safety would be permitted to enforce the provisions of this bill.

THE SENATE S.B. NO. 2115
TWENTY-NINTH LEGISLATURE, 2018
STATE OF HAWAII

A BILL FOR AN ACT

relating to cosmetics.

BE IT ENACTED BY THE LEGISLATURE OF THE STATE OF HAWAII:

SECTION 1. Chapter 328, Hawaii Revised Statutes, is amended by adding a new section to part I to be appropriately designated and to read as follows:

"**§328- Cosmetics; animal testing; prohibition.** (a) Notwithstanding any other law to the contrary, it shall be unlawful for any cosmetic manufacturer to knowingly import for profit, sell at retail, or offer for sale at retail in this State, any cosmetic if the final product or any component thereof was developed or manufactured through use of animal testing that was performed on or after January 1, 2020.

(b) This section shall only apply to ingredients used predominantly for cosmetics.

(c) Any violation of this section shall be punishable by a fine of not more than $500 for the first violation and a fine of not more than $1,000 for each subsequent violation.

(d) Violations of this section shall be prosecuted by the attorney general or prosecutor of the county in which the violation occurred.

(e) When prosecuting a violation of this section pursuant to subsection (d), the attorney general or prosecutor may review the testing data upon which a cosmetic manufacturer has relied in the development or manufacturing of any cosmetic product sold in the State.

(f) For purposes of this section:

"Animal testing" means the internal or external application or exposure of any cosmetic to the skin, eyes, or other body part of a live non-human vertebrate for the purposes of evaluating the safety or efficacy of a cosmetic.

"Cosmetic" means:

(1) Articles intended to be rubbed, poured, sprinkled, or sprayed on, introduced into, or otherwise applied to the human body or any part thereof for cleansing, beautifying, promoting attractiveness, or altering the appearance, including but not limited to personal hygiene products such as deodorant, shampoo, or conditioner; or

(2) Articles intended for use as a component of any such articles.

"Cosmetic manufacturer" means any individual, partnership, corporation, association, or other legal relationship that produces cosmetics that are sold or offered for sale in this State."

SECTION 2. This Act does not affect rights and duties that matured, penalties that were incurred, and proceedings that were begun before its effective date.

SECTION 3. New statutory material is underscored.

SECTION 4. This Act shall take effect on January 1, 2020.

INTRODUCED BY: _____

SB-1249 Animal testing: cosmetics. (2017-2018)

Current Version: 09/28/18 - Chaptered **Compared to Version:** 02/15/18 - Introduced Compare Versions

SECTION 1. Section 1834.9.5 is added to the Civil Code, to read:

1834.9.5. (a) Notwithstanding any other law, it is unlawful for ~~any cosmetic~~ *a* manufacturer to ~~knowingly~~ import for profit, ~~sell at retail,~~ *sell,* or offer for sale ~~at retail~~ in this state, any ~~cosmetic~~ *cosmetic,* if the ~~final product or any component thereof~~ *cosmetic* was developed or manufactured using ~~animal testing~~ *an animal test that was conducted or contracted by the manufacturer, or any supplier of the manufacturer, on or* after January 1, 2020.

(b) For purposes of this section, the following terms apply:

(1) ~~"Cosmetic" means both of the following:~~ *"Animal test" means the internal or external application of a cosmetic, either in its final form or any ingredient thereof, to the skin, eyes, or other body part of a live, nonhuman vertebrate.*

~~(A)~~ *(2)* ~~Any~~ *"Cosmetic" means any* article intended to be rubbed, poured, sprinkled, or sprayed on, introduced into, or otherwise applied to the human body or any part thereof for cleansing, beautifying, promoting attractiveness, or altering the appearance, including, but not limited to, personal hygiene products such as deodorant, shampoo, or conditioner.

~~(B)~~ *(3)* ~~Any article intended for use as a component of an article described in subparagraph (A).~~ *"Ingredient" means any component of a cosmetic as defined by Section 700.3 of Title 21 of the Code of Federal Regulations.*

(4) "Manufacturer" means any person whose name appears on the label of a cosmetic product pursuant to the requirements of Section 701.12 of Title 21 of the Code of Federal Regulations.

(5) "Supplier" means any entity that supplies, directly or through a third party, any ingredient used in the formulation of a manufacturer's cosmetic.

(c) The prohibitions in subdivision (a) do not apply to the following:

(1) An animal test of any cosmetic that is required by a federal or state regulatory authority if all of the following apply:

(A) The ingredient is in wide use and cannot be replaced by another ingredient capable of performing a similar function.

(B) A specific human health problem is substantiated and the need to conduct animal tests is justified and is supported by a detailed research protocol proposed as the basis for the evaluation.

(C) There is not a nonanimal alternative method accepted for the relevant endpoint by the relevant federal or state regulatory authority.

(2) ~~"Cosmetic manufacturer" means any individual, partnership, corporation, association, or other legal relationship that produces cosmetics that are sold or offered for sale in this state.~~ *An animal test that was conducted to comply with a requirement of a foreign regulatory authority, if no evidence derived from the test was relied upon to substantiate the safety of the cosmetic sold in California by the manufacturer.*

(3) ~~"Tested on animals" or "annual testing" means the internal or external application or exposure of a cosmetic to the skin, eyes, or other body part of a live, nonhuman vertebrate for the purpose of evaluating the safety or efficacy of a cosmetic.~~ *An animal test that was conducted on any product or ingredient subject to the requirements of Chapter V of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 351 et seq.).*

(4) An animal test that was conducted for noncosmetic purposes in response to a requirement of a federal, state, or foreign regulatory authority, if no evidence derived from the test was relied upon to substantiate the safety of the cosmetic sold in California by the manufacturer. A manufacturer is not prohibited from reviewing, assessing, or retaining evidence from an animal test conducted pursuant to this paragraph.

~~(c)~~ *(d)* A violation of this section shall be punishable by a fine ~~not to exceed five hundred dollars ($500) for the first violation and not to exceed~~ *of five thousand dollars ($5,000) and an additional* one thousand dollars ($1,000) for each ~~subsequent violation.~~ *day the violation continues.*

~~(d)~~ *(e)* A ~~person or entity that violates~~ *violation of* this section may be ~~prosecuted~~ *enforced* by the district attorney of the county in which the violation occurred, or by the city attorney of the city in which the violation occurred. *The civil fine shall be paid to the entity that is authorized to bring the action.*

~~(e)~~ *(f)* A district attorney or city attorney may, ~~but is not required to,~~ *upon a determination that there is a reasonable likelihood of a violation of this section,* review the testing data upon which a cosmetic manufacturer has relied in the development or manufacturing of ~~any~~ *the relevant* cosmetic ~~products~~ *product* sold in the state. *Information provided under this section shall be protected as a trade secret as defined in subdivision (d) of Section 3426.1. Consistent with the procedures described in Section 3426.5, a district attorney or city attorney shall enter a protective order with a manufacturer before receipt of information from a manufacturer pursuant to this section, and shall take other appropriate measures necessary to preserve the confidentiality of information provided pursuant to this section.*

(g) This section shall not apply to either of the following:

~~(f)~~ *(1)* ~~This section does not apply to a cosmetic~~ *A cosmetic,* if the cosmetic, ~~or any compound of the cosmetic, was~~ *in its final form, was sold in California or* tested on animals prior to January 1, 2020, even if the cosmetic is manufactured after that date.

(2) An ingredient, if the ingredient was sold in California or tested on animals prior to January 1, 2020, even if the ingredient is manufactured after that date.

(h) Notwithstanding any other provision of this section, cosmetic inventory found to be in violation of this section may be sold for a period of 180 days.

(i) No county or political subdivision of the state may establish or continue any prohibition on or relating to animal tests, as defined in this section, that is not identical to the prohibitions set forth in this section and that does not include the exemptions contained in subdivision (c).

~~(g)~~ *(j)* This section shall become operative on January 1, 2020.

SB-1249 Animal testing: cosmetics. (2017-2018)

Date Published: 09/28/2018 09:00 PM

Senate Bill No. 1249

CHAPTER 899

An act to add Section 1834.9.5 to the Civil Code, relating to animal testing.

[Approved by Governor September 28, 2018. Filed with Secretary of State September 28, 2018.]

LEGISLATIVE COUNSEL'S DIGEST

SB 1249, Galgiani. Animal testing: cosmetics.

Existing law prohibits manufacturers and contract testing facilities from using traditional animal testing methods within this state when an appropriate alternative test method has been scientifically validated and recommended by the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) or other specified agencies.

This bill would make it unlawful for a manufacturer to import for profit, sell, or offer for sale in this state, any cosmetic, as defined, if the cosmetic was developed or manufactured using an animal test that was conducted or contracted by the manufacturer, or any supplier of the manufacturer, on or after January 1, 2020, except as specified. The bill would specify that a violation of its provisions is punishable by an initial fine of $5,000 and an additional fine of $1,000 for each day the violation continues, and may be enforced by the district attorney or city attorney in the county or city in which the violation occurred, as specified. The bill would not apply to a cosmetic in its final form or to an ingredient, if the cosmetic or ingredient was sold in California or tested on animals before January 1, 2020, as specified. The bill would authorize cosmetic inventory in violation of the bill's provisions to be sold for a period of 180 days. The bill would prohibit a county or political subdivision of the state from establishing or continuing any prohibition on or relating to animal tests that is not identical to the prohibitions in the bill and that does not include the exemptions contained in the bill.

Vote: majority Appropriation: no Fiscal Committee: no Local Program: no

THE PEOPLE OF THE STATE OF CALIFORNIA DO ENACT AS FOLLOWS:

SECTION 1. Section 1834.9.5 is added to the Civil Code, to read:

1834.9.5. (a) Notwithstanding any other law, it is unlawful for a manufacturer to import for profit, sell, or offer for sale in this state, any cosmetic, if the cosmetic was developed or manufactured using an animal test that was conducted or contracted by the manufacturer, or any supplier of the manufacturer, on or after January 1, 2020.

(b) For purposes of this section, the following terms apply:

(1) "Animal test" means the internal or external application of a cosmetic, either in its final form or any ingredient thereof, to the skin, eyes, or other body part of a live, nonhuman vertebrate.

(2) “Cosmetic” means any article intended to be rubbed, poured, sprinkled, or sprayed on, introduced into, or otherwise applied to the human body or any part thereof for cleansing, beautifying, promoting attractiveness, or altering the appearance, including, but not limited to, personal hygiene products such as deodorant, shampoo, or conditioner.

(3) “Ingredient” means any component of a cosmetic as defined by Section 700.3 of Title 21 of the Code of Federal Regulations.

(4) “Manufacturer” means any person whose name appears on the label of a cosmetic product pursuant to the requirements of Section 701.12 of Title 21 of the Code of Federal Regulations.

(5) “Supplier” means any entity that supplies, directly or through a third party, any ingredient used in the formulation of a manufacturer’s cosmetic.

(c) The prohibitions in subdivision (a) do not apply to the following:

(1) An animal test of any cosmetic that is required by a federal or state regulatory authority if all of the following apply:

(A) The ingredient is in wide use and cannot be replaced by another ingredient capable of performing a similar function.

(B) A specific human health problem is substantiated and the need to conduct animal tests is justified and is supported by a detailed research protocol proposed as the basis for the evaluation.

(C) There is not a nonanimal alternative method accepted for the relevant endpoint by the relevant federal or state regulatory authority.

(2) An animal test that was conducted to comply with a requirement of a foreign regulatory authority, if no evidence derived from the test was relied upon to substantiate the safety of the cosmetic sold in California by the manufacturer.

(3) An animal test that was conducted on any product or ingredient subject to the requirements of Chapter V of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 351 et seq.).

(4) An animal test that was conducted for noncosmetic purposes in response to a requirement of a federal, state, or foreign regulatory authority, if no evidence derived from the test was relied upon to substantiate the safety of the cosmetic sold in California by the manufacturer. A manufacturer is not prohibited from reviewing, assessing, or retaining evidence from an animal test conducted pursuant to this paragraph.

(d) A violation of this section shall be punishable by a fine of five thousand dollars ($5,000) and an additional one thousand dollars ($1,000) for each day the violation continues.

(e) A violation of this section may be enforced by the district attorney of the county in which the violation occurred, or by the city attorney of the city in which the violation occurred. The civil fine shall be paid to the entity that is authorized to bring the action.

(f) A district attorney or city attorney may, upon a determination that there is a reasonable likelihood of a violation of this section, review the testing data upon which a cosmetic manufacturer has relied in the development or manufacturing of the relevant cosmetic product sold in the state. Information provided under this section shall be protected as a trade secret as defined in subdivision (d) of Section 3426.1. Consistent with the procedures described in Section 3426.5, a district attorney or city attorney shall enter a protective order with a manufacturer before receipt of information from a manufacturer pursuant to this section, and shall take other appropriate measures necessary to preserve the confidentiality of information provided pursuant to this section.

(g) This section shall not apply to either of the following:

(1) A cosmetic, if the cosmetic, in its final form, was sold in California or tested on animals prior to January 1, 2020, even if the cosmetic is manufactured after that date.

(2) An ingredient, if the ingredient was sold in California or tested on animals prior to January 1, 2020, even if the ingredient is manufactured after that date.

(h) Notwithstanding any other provision of this section, cosmetic inventory found to be in violation of this section may be sold for a period of 180 days.

(i) No county or political subdivision of the state may establish or continue any prohibition on or relating to animal tests, as defined in this section, that is not identical to the prohibitions set forth in this section and that does not include the exemptions contained in subdivision (c).

(j) This section shall become operative on January 1, 2020.

Talcum Powder Products Litigation

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Cosmetics Products Liability

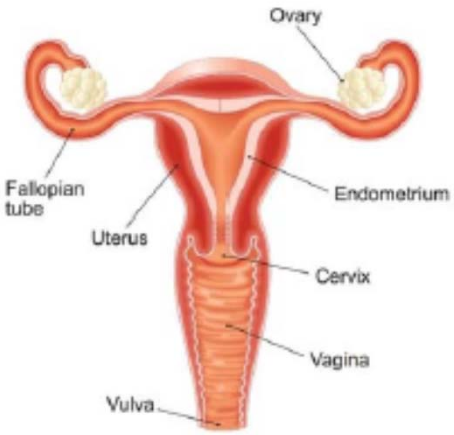
In re Johnson & Johnson Talcum Powder Products Marketing, Sales Practices, and Products Liability Litigation, District of New Jersey

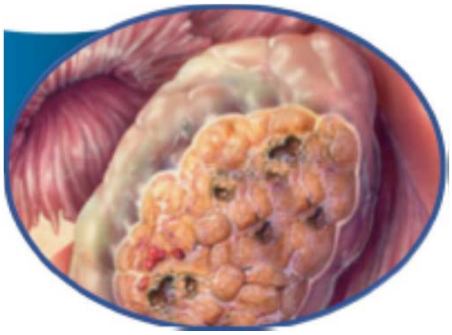
Victoria J. Maniatis, Esq., Partner
Phillips Sanders Grossman LLC, Garden City, NY

Overview of Presentation

- Ovarian Cancer
- Talc
- Regulatory Framework
- FDA and other Regulatory Agencies
- Failure to Warn

Ovarian Cancer





Types of Ovarian Cancers

- Epithelial Ovarian Cancer
  - Serous – 90%
  - Mucinous
  - Borderline tumors
  - Endometrioid
  - Clear Cell
- Others

FIGO Staging Of Ovarian Cancer

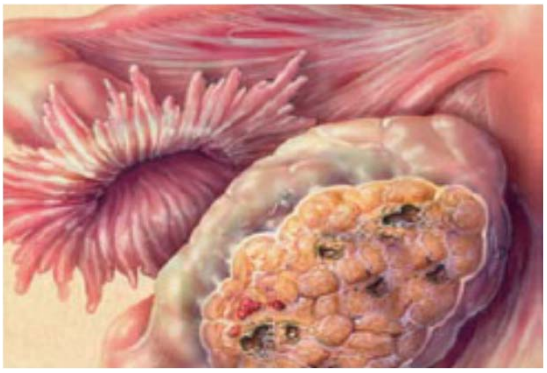
Stage	5-Year Survival (%)
IA	94%
IB	92%
IC	85%
IIA	78%
IIB	73%
IIIA	59%
IIIB	52%
IIIC	39%
IV	17%

Incidence of Ovarian Cancer

- Second most common gynecologic malignancy
- Most common cause of gynecologic cancer; fifth leading cause of cancer death in women
- In the U.S., there are approximately 22,000 new cases and 14,000 cancer-related deaths each year.
- The majority of ovarian cancer patients are diagnosed at an advanced stage.
- 10-11% of ovarian cancers are attributable to genital use of talc (Cramer 1999)

Factors That Increase Risk of Epithelial Ovarian Cancer

- Use of Talc in genital area
- BRCA gene positive
- Age
- Infertility
- Endometriosis
- Polycystic ovarian syndrome
- IUD use
- Smoking
- Family history
- HRT



Talc as a Cosmetic Product

- Talc is used in cosmetic products for feminine hygiene and baby powders
- Talc was introduced as a baby powder by Johnson & Johnson in 1894
- Types of application of baby powders vary and historically applied perineally, on napkins, tampons, condoms, and underwear
- Refers to both mineral talc and industrial mineral products, marketed under the name talc
- As a mineral, talc produces an irritant and inflammatory response at sites of exposure

What is Talc?

- Main Substance in Talcum Powder
- Magnesium Trisilicate
- H2Mg3 (SiO3)4 or Mg3Si4O10 (OH) 2
- Mined from the earth
- Mg:SiAtomic % = .75Weight % = .65

Who Are The Defendants?

- Johnson & Johnson
- Johnson & Johnson Consumer Inc., f/k/n J&J Consumer Companies Inc.
  - Subsidiary of J&J
  - Manufacturer, seller and distributor of finished talc body powder products
- Imerys Talc America, Inc., f/k/a Luzenac America
  - Talc ingredient manufacturer and supplier

Rules of Road

- Talcum powder is a cosmetic product
- Cosmetics products like talc do not require FDA approval
- Cosmetics manufacturers are legally responsible for ensuring that its product and ingredients are safe for use.
- Cosmetics manufacturers are not required to test to demonstrate safety
- Cosmetics manufacturers are not required to share safety information with the FDA

➔No FDA Approval, No Risk-Benefit Analysis

21 CFR 740.1(a) – Regulatory Standard

TITLE 21--FOOD AND DRUGS
CHAPTER I--FOOD AND DRUG ADMINISTRATION
DEPARTMENT OF HEALTH AND HUMAN SERVICES
SUBCHAPTER G--COSMETICS
PART 740 -- COSMETIC PRODUCT WARNING STATEMENTS

Subpart A--General

Sec. 740.1 Establishment of warning statements.

(a) The label of a cosmetic product shall bear a warning statement whenever necessary or appropriate to prevent a health hazard that may be associated with the product.

(b) The Commissioner of Food and Drugs, either on his own initiative or on behalf of any interested person who has submitted a petition, may publish a proposal to establish or amend, under subpart B of this part, a regulation prescribing a warning for a cosmetic. Any such petition shall include an adequate factual basis to support the petition, shall be in the form set forth in part 10 of this chapter, and will be published for comment if it contains reasonable grounds for the proposed regulation.

[40 FR 8917, Mar. 3, 1975, as amended at 42 FR 15676, Mar. 22, 1977]

New Jersey Product Liability Law

- Defendant liable if the defect, whatever it is found to be, must have been a proximate cause of the accident.
- Proximate cause means that the defect in the product was a substantial factor which singly, or in combination with another cause, brought about the accident.
- Plaintiff need not prove that ovarian cancer could have been anticipated so long as it was within the realm of foreseeability that some harm could result from the defect in question.

From N.J. Charge 5.40I

New Jersey Product Liability Law: A relative risk of 2.0 is not required

- A relative risk of 2.0 is not so much a password to a finding of causation as one piece of evidence, among others, for the court to consider in determining whether the expert has employed sound methodology in reaching his or her conclusion." Landrigan v. Celotex Corp., 127 N.J. 404, 419 (1992) (asbestos exposure case).
- "In Landrigan [. . .], we rejected the proposition that epidemiological studies must show a relative risk in excess of 2.0 before an expert may draw an inference that a particular person's disease was caused by exposure to a harmful substance." Caterinicchio v. Pittsburgh Cornign Corp., 127 N.J. 428, 434 (1992) (toxic tort case).
- "Where, however, study after study has shown some positive correlation, although not to the factor of 2.0, it might be said that asbestos is at least a producing factor in some colon cancers, even if the precise biological process has not yet been defines. . . . [A] qualified expert may view the epidemiological studies and factor out other known risk factors . . . or other factors which might enhance the remaining risks, even though the risk in the study fell short of the 2.0 correlation." Grassis v. Johns-Manville Corp., 591 A.2d 671, 675 (N.J. Sup. Ct. App. Div. 1991) (asbestos exposure case).

Totality of Evidence

- Cancer Biology Research & Experience
- Laboratory Studies
- Animal Studies
- Pathology
- Toxicology
- Epidemiology Studies & Human Data
- Regulatory & Advisory Bodies

Totality of Evidence

- Epidemiologic studies demonstrate a statistically significant increase in the risk of epithelial ovarian cancer for “ever” v. “never” perineal use of talc powders
- Risk estimates of the Case-control studies are consistent and compatible with the several Meta-analyses and Pooled studies
- 3 Cohort studies; one of which demonstrates a statistically significant increase in risk with serous ovarian cancer
- Evidence supports dose-response when appropriate metrics of frequency and duration of exposure are assessed
- Significant evidence that talc can migrate to the upper genital tract and ovaries
- Biologically plausible mechanisms of talc’s carcinogenicity are widely accepted

Totality of Evidence: NTP, CPC, NCI, FDA

- National Toxicology Program (NTP) 1992: Clear evidence of cardiogenic activity in female rats
- Cancer Prevention Coalition (CPC) 1994: "Women have the unarguable right to know" about the association between talc and ovarian cancer, and urged J&J to withdraw talc-containing products, or substitute talc with a safer alternative (cornstarch), or include in the label information about the risk of ovarian cancer.

Totality of Evidence: NCI

- Journal of the National Cancer Institute, Vol. 91, No. 17, September 1, 1999 included talc exposure as a risk factor for ovarian cancer.
- March 19, 2015: Based on solid evidence, perineal application of talc is associated with a small increased risk of ovarian cancer. The International Agency for Research on Cancer has concluded that perineal talc is a possible carcinogen… Talcum powder dusted on the perineum may reach the ovaries by entering the vagina.
- Also acknowledged a "well-conducted" study of talc linked to ovarian cancer risk in African-American women
- But on May 4, 2015, it maintained: Studies of women who used talcum powder (talc) dusted on the perineum have not found clear evidence of an increased risk of ovarian cancer.

FDA Letter (April 1, 2014) in response to Citizen's Petitions of November 17, 1994 and May 13, 2008 requesting that the FDA require a cancer warning on cosmetic talc products

While there exists no direct proof of talc and ovarian carcinogenesis, the potential for particulates to migrate from the perineum and vagina to the peritoneal cavity is indisputable. It is, therefore, plausible that perineal talc (and other particulate) that reaches the endometrial cavity, Fallopian Tubes, ovaries and peritoneum may elicit a foreign body type reaction and inflammatory response that, in some exposed women, may progress to epithelial cancers. However, there has been no conclusive evidence to support causality.

The best evidence for an association or causal relationship between genital talc exposure and ovarian cancer comes from epidemiologic data which show a statistically significant but modest increased risk of epithelial ovarian cancer, especially with serous histology, among women with a history of genital dusting with talcum powder. While the growing body of evidence to support a possible association between genital talc exposure and serous ovarian cancer is difficult to dismiss, the evidence is insufficient for FDA to require as definitive a warning as you are seeking.

Institute of Medicine (IOM) (2016)

response. The use of perineal talcum powder has been associated with a 20 to 30 percent increased risk of ovarian cancer, although it also has been show to vary by histologic subtype (Cramer et al., 2015; Terry et al., 2013).

[Code of Federal Regulations]
[Title 21, Volume 7]
[Revised as of April 1, 2015]
[CITE: 21CFR740.1]

Sec. 740.1 Establishment of warning statements.

(a) The label of a cosmetic product shall bear a warning statement whenever necessary or appropriate to prevent a health hazard that may be associated with the product.

Law on Failure to Warn

5.40C FAILURE TO WARN/INSTRUCT (Approved 3/00; Revised 10/01)

If a product fails to contain an adequate warning or instructions, it is defective. *[Plaintiff]* says the *[Product]* did not contain an adequate warning or instruction because *[insert short factual description of plaintiff's contention why the warning was inadequate]*. *[Defendant]* says the *[Product]* did contain an adequate warning or instruction because *[insert short factual description]*.

The *[Defendant]* as the manufacturer or seller of a product had a duty to provide adequate warnings or instructions about the dangers the *[Product]* may present. *[Defendant]* had this duty even if the *[Product]* were perfectly designed and manufactured. To decide the plaintiff's failure to warn claim you must determine what warnings and instructions the defendant provided and whether those warnings and instructions were adequate.

Did Defendants Take Responsible Steps to Warn the Public?

Did Defendants Take Responsible Steps to Warn the Public?

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Title 21: Food and Drugs

PART 700—GENERAL

Contents

AUTHORITY: 21 U.S.C. 321, 331, 352, 355, 361, 362, 371, 374.

SOURCE: 39 FR 10054, Mar. 15, 1974, unless otherwise noted.

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Subpart A—General Provisions

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§700.3 Definitions.

As used in this subchapter:

(a) The term *act* means the Federal Food, Drug, and Cosmetic Act.

(b) The term *cosmetic product* means a finished cosmetic the manufacture of which has been completed. Any cosmetic product which is also a drug or device or component thereof is also subject to the requirements of Chapter V of the act.

(c) The term *flavor* means any natural or synthetic substance or substances used solely to impart a taste to a cosmetic product.

(d) The term *fragrance* means any natural or synthetic substance or substances used solely to impart an odor to a cosmetic product.

(e) The term *ingredient* means any single chemical entity or mixture used as a component in the manufacture of a cosmetic product.

(f) The term *proprietary ingredient* means any cosmetic product ingredient whose name, composition, or manufacturing process is protected from competition by secrecy, patent, or copyright.

(g) The term *chemical description* means a concise definition of the chemical composition using standard chemical nomenclature so that the chemical structure or structures of the components of the ingredient would be clear to a practicing chemist. When the composition cannot be described chemically, the substance shall be described in terms of its source and processing.

(h) The term *cosmetic raw material* means any ingredient, including an ingredient that is a mixture, which is used in the manufacture of a cosmetic product for commercial distribution and is supplied to a cosmetic product manufacturer, packer, or distributor by a cosmetic raw material manufacturer or supplier.

(i) The term *commercial distribution* of a cosmetic product means annual gross sales in excess of $1,000 for that product.

(j) *Establishment* means a place of business where cosmetic products are manufactured or packaged.

(k) The term *manufacture* of a cosmetic product means the making of any cosmetic product by chemical, physical, biological, or other procedures, including manipulation, sampling, testing, or control procedures applied to the product.

(l) The term *packaging* of a cosmetic product means filling or labeling the product container, including changing the immediate container or label (but excluding changing other labeling) at any point in the distribution of the cosmetic product from the original place of manufacture to the person who makes final delivery or sale to the ultimate consumer.

(m) The term *all business trading names used by the establishment* means any name which is used on a cosmetic product label and owned by the cosmetic product manufacturer or packer, but is different from the principal name under which the cosmetic product manufacturer or packer is registered.

(n) The definitions and interpretations contained in sections 201, 601, and 602 of the act shall be applicable to such terms when used in the regulations in this subchapter.

(o) *System of commercial distribution* of a cosmetic product means any distribution outside the establishment manufacturing the product, whether for sale, to promote future sales (including free samples of the product), or to gage consumer acceptance through market testing, in excess of $1,000 in cost of goods.

(p) *Filed screening procedure* means a procedure that is:

(1) On file with the Food and Drug Administration and subject to public inspection;

(2) Designed to determine that there is a reasonable basis for concluding that an alleged injury did not occur in conjunction with the use of the cosmetic product; and

(3) Which is subject, upon request by the Food and Drug Administration, to an audit conducted by the Food and Drug Administration at reasonable times and, where an audit is conducted, such audit shows that the procedure is consistently being applied and that the procedure is not disregarding reportable information.

(q) *Reportable experience* means an experience involving any allergic reaction, or other bodily injury, alleged to be the result of the use of a cosmetic product under the conditions of use prescribed in the labeling of the product, under such conditions of use as are customary or reasonably foreseeable for the product or under conditions of misuse, that has been reported to the manufacturer, packer, or distributor of the product by the affected person or any other person having factual knowledge of the incident, other than an alleged experience which has been determined to be unfounded or spurious when evaluated by a filed screening procedure.

[39 FR 10054, Mar. 15, 1974, as amended at 46 FR 38073, July 24, 1981]

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Subpart B—Requirements for Specific Cosmetic Products

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§700.11 Cosmetics containing bithionol.

(a) Bithionol has been used to some extent as an antibacterial agent in cosmetic preparations such as detergent bars, shampoos, creams, lotions, and bases used to hide blemishes. New evidence of clinical experience and photopatch tests indicate that bithionol is capable of causing photosensitivity in man when used topically and that in some instances the photosensitization may persist for prolonged periods as severe reactions without further contact with sensitizing articles. Also, there is evidence to indicate that bithionol may produce cross-sensitization with other commonly used chemicals such as certain halogenated salicylanilides and hexachlorophene. It is, therefore, the view of the Food and Drug Administration that

bithionol is a deleterious substance which may render any cosmetic product that contains it injurious to users. Accordingly, any cosmetic containing bithionol is deemed to be adulterated under section 601(a) of the Federal Food, Drug, and Cosmetic Act.

(b) Regulatory proceedings may be initiated with respect to any cosmetic preparation containing bithionol shipped within the jurisdiction of the act after March 15, 1968.

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§700.13 Use of mercury compounds in cosmetics including use as skinbleaching agents in cosmetic preparations also regarded as drugs.

(a) Mercury-containing cosmetic preparations have been represented for many years as skin-bleaching agents or as preparations to remove or prevent freckles and/or brown spots (so-called age spots). Preparations intended for such use are regarded as drugs as well as cosmetics. In addition to such use as skin-bleaching agents, mercury compounds have also been widely used as preservatives in cosmetics such as hand and body creams and lotions; hair shampoos, hair sets and rinses, hair straighteners, hair coloring, and other preparations; bath oils, bubble bath, and other bath preparations; makeup; antiperspirants and deodorants; and eye-area cosmetics.

(b) The toxicity of mercury compounds is extensively documented in scientific literature. It is well known that mercury compounds are readily absorbed through the unbroken skin as well as through the lungs by inhalation and by intestinal absorption after ingestion. Mercury is absorbed from topical application and is accumulated in the body, giving rise to numerous adverse effects. Mercury is a potent allergen and sensitizer, and skin irritation is common after topical application. Cosmetic preparations containing mercury compounds are often applied with regularity and frequency for prolonged periods. Such chronic use of mercury-containing skin-bleaching preparations has resulted in the accumulation of mercury in the body and the occurrence of severe reactions. Recently it has also been determined that microorganisms in the environment can convert various forms of mercury into highly toxic methyl mercury which has been found in the food supply and is now considered to be a serious environmental problem.

(c) The effectiveness of mercury-containing preparations as skin-bleaching agents is questionable. The Food and Drug Administration has not been provided with well controlled studies to document the effectiveness of these preparations. Although mercurial preservatives are recognized as highly effective, less toxic and satisfactory substitutes are available except in the case of certain eye-area cosmetics.

(d) Because of the known hazards of mercury, its questionable efficacy as a skin-bleaching agent, and the availability of effective and less toxic nonmercurial preservatives, there is no justification for the use of mercury in skin-bleaching preparations or its use as a preservative in cosmetics, with the exception of eye-area cosmetics for which no other effective and safe nonmercurial preservative is available. The continued use of mercurial preservatives in such eye-area cosmetics is warranted because mercury compounds are exceptionally effective in preventing *Pseudomonas* contamination of cosmetics and *Pseudomonas* infection of the eye can cause serious injury, including blindness. Therefore:

(1) The Food and Drug Administration withdraws the opinion expressed in trade correspondence TC-9 (issued May 13, 1939) and concludes that any product containing mercury as a skin-bleaching agent and offered for sale as skin-bleaching, beauty, or facial preparation is misbranded within the meaning of sections 502(a), 502(f)(1) and (2), and 502(j), and may be a new drug without approval in violation of section 505 of the Federal Food, Drug, and Cosmetic Act. Any such preparation shipped within the jurisdiction of the Act after January 5, 1973 will be the subject of regulatory action.

(2) The Food and Drug Administration withdraws the opinion expressed in trade correspondence TC-412 (issued Feb. 11, 1944) and will regard as adulterated within the meaning of section 601(a) of the Act any cosmetic containing mercury unless the cosmetic meets the conditions of paragraph (d)(2) (i) or (ii) of this section.

(i) It is a cosmetic containing no more than a trace amount of mercury and such trace amount is unavoidable under conditions of good manufacturing practice and is less than 1 part per million (0.0001 percent), calculated as the metal; or

(ii) It is a cosmetic intended for use only in the area of the eye, it contains no more than 65 parts per million (0.0065 percent) of mercury, calculated as the metal, as a preservative, and there is no effective and safe nonmercurial substitute preservative available for use in such cosmetic.

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§700.14 Use of vinyl chloride as an ingredient, including propellant of cosmetic aerosol products.

(a) Vinyl chloride has been used as an ingredient in cosmetic aerosol products including hair sprays. Where such aerosol products are used in the confines of a small room, as is often the case, the level of vinyl chloride to which the individual may be exposed could be significantly in excess of the safe level established in connection with occupational exposure. Evidence indicates that vinyl chloride inhalation can result in acute toxicity, manifested by dizziness, headache, disorientation, and

unconsciousness where inhaled at high concentrations. Studies also demonstrate carcinogenic effects in animals as a result of inhalation exposure to vinyl chloride. Furthermore, vinyl chloride has recently been linked to liver disease, including liver cancer, in workers engaged in the polymerization of vinyl chloride. It is the view of the Commissioner that vinyl chloride is a deleterious substance which may render any cosmetic aerosol product that contains it as an ingredient injurious to users. Accordingly, any cosmetic aerosol product containing vinyl chloride as an ingredient is deemed to be adulterated under section 601(a) of the Federal Food, Drug, and Cosmetic Act.

(b) Any cosmetic aerosol product containing vinyl chloride as an ingredient shipped within the jurisdiction of the Act is subject to regulatory action.

[39 FR 30830, Aug. 26, 1974]

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§700.15 Use of certain halogenated salicylanilides as ingredients in cosmetic products.

(a) Halogenated salicylanilides (tribromsalan (TBS,3,4′,5-tribromosalicylanilide), dibromsalan (DBS,4′5-dibromosalicylanilide), metabromsalan (MBS, 3,5-dibromosalicylanilide) and 3,3′,4,5′-tetrachlorosalicylanilide (TCSA)) have been used as antimicrobial agents for a variety of purposes in cosmetic products. These halogenated salicylanilides are potent photosensitizers and cross-sensitizers and can cause disabling skin disorders. In some instances, the photosensitization may persist for prolonged periods as a severe reaction without further exposure to these chemicals. Safer alternative antimicrobial agents are available.

(b) These halogenated salicylanilides are deleterious substances which render any cosmetic that contains them injurious to users. Therefore, any cosmetic product that contains such a halogenated salicylanilide as an ingredient at any level for any purpose is deemed to be adulterated under section 601(a) of the Federal Food, Drug, and Cosmetic Act.

(c) Any cosmetic product containing these halogenated salicylanilides as an ingredient that is initially introduced into interstate commerce after December 1, 1975, that is not in compliance with this section is subject to regulatory action.

[40 FR 50531, Oct. 30, 1975]

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§700.16 Use of aerosol cosmetic products containing zirconium.

(a) Zirconium-containing complexes have been used as an ingredient in cosmetics and/or cosmetics that are also drugs, as, for example, aerosol antiperspirants. Evidence indicates that certain zirconium compounds have caused human skin granulomas and toxic effects in the lungs and other organs of experimental animals. When used in aerosol form, some zirconium will reach the deep portions of the lungs of users. The lung is an organ, like skin, subject to the development of granulomas. Unlike the skin, the lung will not reveal the presence of granulomatous changes until they have become advanced and, in some cases, permanent. It is the view of the Commissioner that zirconium is a deleterious substance that may render any cosmetic aerosol product that contains it injurious to users.

(b) Any aerosol cosmetic product containing zirconium is deemed to be adulterated under section 601(a) of the Federal Food, Drug, and Cosmetic Act.

(c) Any such cosmetic product introduced in interstate commerce after September 15, 1977 is subject to regulatory action.

[42 FR 41376, Aug. 16, 1977]

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§700.18 Use of chloroform as an ingredient in cosmetic products.

(a) Chloroform has been used as an ingredient in cosmetic products. Recent information has become available associating chloroform with carcinogenic effects in animals. Studies conducted by the National Cancer Institute have demonstrated that the oral administration of chloroform to mice and rats induced hepatocellular carcinomas (liver cancer) in mice and renal tumors in male rats. Scientific literature indicates that chloroform is absorbed from the gastrointestinal tract, through the respiratory system, and through the skin. The Commissioner concludes that, on the basis of these findings, chloroform is a deleterious substance which may render injurious to users any cosmetic product that contains chloroform as an ingredient.

(b) Any cosmetic product containing chloroform as an ingredient is adulterated and is subject to regulatory action under sections 301 and 601(a) of the Federal Food, Drug, and Cosmetic Act. Any cosmetic product containing chloroform in residual amounts from its use as a processing solvent during manufacture, or as a byproduct from the synthesis of an ingredient, is not, for the purpose of this section, considered to contain chloroform as an ingredient.

[41 FR 26845, June 29, 1976]

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§700.19 Use of methylene chloride as an ingredient of cosmetic products.

(a) Methylene chloride has been used as an ingredient of aerosol cosmetic products, principally hair sprays, at concentrations generally ranging from 10 to 25 percent. In a 2-year animal inhalation study sponsored by the National Toxicology Program, methylene chloride produced a significant increase in benign and malignant tumors of the lung and liver of male and female mice. Based on these findings and on estimates of human exposure from the customary use of hair sprays, the Food and Drug Administration concludes that the use of methylene chloride in cosmetic products poses a significant cancer risk to consumers, and that the use of this ingredient in cosmetic products may render these products injurious to health.

(b) Any cosmetic product that contains methylene chloride as an ingredient is deemed adulterated and is subject to regulatory action under sections 301 and 601(a) of the Federal Food, Drug, and Cosmetic Act.

[54 FR 27342, June 29, 1989]

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§700.23 Chlorofluorocarbon propellants.

The use of chlorofluorocarbons in cosmetics as propellants in self-pressurized containers is prohibited as provided in §2.125 of this chapter.

[43 FR 11317, Mar. 17, 1978]

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§700.25 Tamper-resistant packaging requirements for cosmetic products.

(a) *General.* Because most cosmetic liquid oral hygiene products and vaginal products are not now packaged in tamper-resistant retail packages, there is the opportunity for the malicious adulteration of those cosmetic products with health risks to individuals who unknowingly purchase adulterated products and with loss of consumer confidence in the security of cosmetic product packages. The Food and Drug Administration has the authority and responsibility under the Federal Food, Drug, and Cosmetic Act (the act) to establish a uniform national requirement for tamper-resistant packaging of cosmetic liquid oral hygiene products or products used vaginally that will improve the packaging security and help assure the safety of those products. Such a cosmetic product for retail sale that is not packaged in a tamper-resistant package or that is not properly labeled under this section is adulterated under section 601 of the act or misbranded under section 602 of the act, or both.

(b) *Requirement for tamper-resistant package.* Each manufacturer and packer who packages a cosmetic liquid oral hygiene product or vaginal product for retail sale shall package the product in a tamper-resistant package, if this product is accessible to the public while held for sale. A tamper-resistant package is one having an indicator or barrier to entry which, if breached or missing, can reasonably be expected to provide visible evidence to consumers that tampering has occurred. To reduce the likelihood of substitution of a tamper-resistant feature after tampering, the indicator or barrier to entry is required to be distinctive by design (e.g., an aerosol product container) or by the use of an identifying characteristic (e.g., a pattern, name, registered trademark, logo, or picture). For purposes of this section, the term “distinctive by design” means the packaging cannot be duplicated with commonly available materials or through commonly available processes. For purposes of this section, the term “aerosol product” means a product which depends upon the power of a liquified or compressed gas to expel the contents from the container. A tamper-resistant package may involve an immediate-container and closure system or secondary-container or carton system or any combination of systems intended to provide a visual indication of package integrity. The tamper-resistant feature shall be designed to and shall remain intact when handled in a reasonable manner during manufacture, distribution, and retail display.

(c) *Labeling.* Each retail package of a cosmetic product covered by this section, except aerosol products as defined in paragraph (b) of this section, is required to bear a statement that is prominently placed so that consumers are alerted to the specific tamper-resistant feature of the package. The labeling statement is also required to be so placed that it will be unaffected if the tamper-resistant feature of the package is breached or missing. If the tamper-resistant feature chosen to meet the requirement in paragraph (b) of this section is one that uses an identifying characteristic, that characteristic is required to be referred to in the labeling statement. For example, the labeling statement on a bottle with a shrink band could say “For your protection, this bottle has an imprinted seal around the neck.”

(d) *Requests for exemptions from packaging and labeling requirements.* A manufacturer or packer may request an exemption from the packaging and labeling requirements of this section. A request for an exemption is required to be submitted

in the form of a citizen petition under §10.30 of this chapter and should be clearly identified on the envelope as a “Request for Exemption from Tamper-resistant Rule.” The petition is required to contain the following:

(1) The name of the product.

(2) The reasons that the product's compliance with the tamper-resistant packaging or labeling requirements of this section is unnecessary or cannot be achieved.

(3) A description of alternative steps that are available, or that the petitioner has already taken, to reduce the likelihood that the product will be the subject of malicious adulteration.

(4) Other information justifying an exemption.

This information collection requirement has been approved by the Office of Management and Budget under number 0910-0149.

(e) *Effective date.* Cosmetic products covered by this section are required to comply with the requirements of this section on the dates listed below except to the extent that a product's manufacturer or packer has obtained an exemption from a packaging or labeling requirement.

(1) *Initial effective date for packaging requirements.* (i) The packaging requirement in paragraph (b) of this section is effective on Feburary 7, 1983 for each affected cosmetic product (except vaginal tablets) packaged for retail sale on or after that date, except for the requirement in paragraph (b) of this section for a distinctive indicator or barrier to entry.

(ii) The packaging requirement in paragraph (b) of this section is effective on May 5, 1983 for each cosmetic product that is a vaginal tablet packaged for retail sale on or after that date.

(2) *Initial effective date for labeling requirements.* The requirement in paragraph (b) of this section that the indicator or barrier to entry be distinctive by design and the requirement in paragraph (c) of this section for a labeling statement are effective on May 5, 1983 for each affected cosmetic product packaged for retail sale on or after that date, except that the requirement for a specific label reference to any identifying characteristic is effective on February 6, 1984 for each affected cosmetic product packaged for retail sale on or after that date.

(3) *Retail level effective date.* The tamper-resistant packaging requirement of paragraph (b) of this section is effective February 6, 1984 for each affected cosmetic product held for sale on or after that date that was packaged for retail sale before May 5, 1983. This does not include the requirement in paragraph (b) of this section that the indicator or barrier to entry be distinctive by design. Products packaged for retail sale after May 5, 1983, as required to be in compliance with all aspects of the regulations without regard to the retail level effective date.

[47 FR 50451, Nov. 5, 1982; 48 FR 1707, Jan. 14, 1983; 48 FR 11427, Mar. 18, 1983, as amended at 48 FR 16664, Apr. 19, 1983; 48 FR 37624, Aug. 19, 1983]

EFFECTIVE DATE NOTE: See 48 FR 41579, Sept. 16, 1983, for a document announcing an interim stay of the effective date of certain provisions in paragraph (e)(3) of §700.25.

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§700.27 Use of prohibited cattle materials in cosmetic products.

(a) *Definitions.* The definitions and interpretations of terms contained in section 201 of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) apply to such terms when used in this part. The following definitions also apply:

(1) *Prohibited cattle materials* mean specified risk materials, small intestine of all cattle except as provided in paragraph (b)(2) of this section, material from nonambulatory disabled cattle, material from cattle not inspected and passed, or mechanically separated (MS) (Beef). Prohibited cattle materials do not include the following:

(i) Tallow that contains no more than 0.15 percent insoluble impurities, tallow derivatives, gelatin, hides and hide-derived products, and milk and milk products, and

(ii) Cattle materials inspected and passed from a country designated under paragraph (e) of this section.

(2) *Inspected and passed* means that the product has been inspected and passed for human consumption by the appropriate regulatory authority, and at the time it was inspected and passed, it was found to be not adulterated.

(3) *Mechanically separated (MS) (Beef)* means a meat food product that is finely comminuted, resulting from the mechanical separation and removal of most of the bone from attached skeletal muscle of cattle carcasses and parts of carcasses that meets the specifications contained in 9 CFR 319.5, the U.S. Department of Agriculture regulation that prescribes the standard of identity for MS (Species).

(4) *Nonambulatory disabled cattle* means cattle that cannot rise from a recumbent position or that cannot walk, including, but not limited to, those with broken appendages, severed tendons or ligaments, nerve paralysis, fractured vertebral column, or metabolic conditions.

(5) *Specified risk material* means the brain, skull, eyes, trigeminal ganglia, spinal cord, vertebral column (excluding the vertebrae of the tail, the transverse processes of the thoracic and lumbar vertebrae, and the wings of the sacrum), and dorsal root ganglia of cattle 30 months of age and older and the tonsils and distal ileum of the small intestine of all cattle.

(6) *Tallow* means the rendered fat of cattle obtained by pressing or by applying any other extraction process to tissues derived directly from discrete adipose tissue masses or to other carcass parts and tissues. Tallow must be produced from tissues that are not prohibited cattle materials or must contain no more than 0.15 percent insoluble impurities as determined by the method entitled “Insoluble Impurities” (AOCS Official Method Ca 3a-46), American Oil Chemists' Society (AOCS), 5th Edition, 1997, incorporated by reference in accordance with 5 U.S.C. 552(a) and 1 CFR part 51, or another method equivalent in accuracy, precision, and sensitivity to AOCS Official Method Ca 3a-46. You may obtain copies of the method from AOCS (*http://www.aocs.org*) 2211 W. Bradley Ave. Champaign, IL 61821. Copies may be examined at the Food and Drug Administration's Main Library, 10903 New Hampshire Ave., Bldg. 2, Third Floor, Silver Spring, MD 20993, 301-796-2039 or at the National Archives and Records Administration (NARA). For information on the availability of this material at NARA, call 202-741-6030, or go to *http://www.archives.gov/federal_register/code_of_federal_regulations/ibr_locations.html.*

(7) *Tallow derivative* means any chemical obtained through initial hydrolysis, saponification, or trans-esterification of tallow; chemical conversion of material obtained by hydrolysis, saponification, or trans-esterification may be applied to obtain the desired product.

(8) *Gelatin* means a product that has been obtained by the partial hydrolysis of collagen derived from hides, connective tissue, and/or bone bones of cattle and swine. Gelatin may be either Type A (derived from an acid-treated precursor) or Type B (derived from an alkali-treated precursor) that has gone through processing steps that include filtration and sterilization or an equivalent process in terms of infectivity reduction.

(b) *Requirements.* (1) No cosmetic shall be manufactured from, processed with, or otherwise contain, prohibited cattle materials.

(2) The small intestine is not considered prohibited cattle material if the distal ileum is removed by a procedure that removes at least 80 inches of the uncoiled and trimmed small intestine, as measured from the caeco-colic junction and progressing proximally towards the jejunum, or by a procedure that the establishment can demonstrate is equally effective in ensuring complete removal of the distal ileum.

(c) *Records.* (1) Manufacturers and processors of a cosmetic that is manufactured from, processed with, or otherwise contains, material from cattle must establish and maintain records sufficient to demonstrate that the cosmetic is not manufactured from, processed with, or does not otherwise contain, prohibited cattle materials.

(2) Records must be retained for 2 years after the date they were created.

(3) Records must be retained at the manufacturing or processing establishment or at a reasonably accessible location.

(4) The maintenance of electronic records is acceptable. Electronic records are considered to be reasonably accessible if they are accessible from an onsite location.

(5) Records required by this section and existing records relevant to compliance with this section must be available to FDA for inspection and copying.

(6) When filing entry with U.S. Customs and Border Protection, the importer of record of a cosmetic manufactured from, processed with, or otherwise containing, cattle material must affirm that the cosmetic was manufactured from, processed with, or otherwise contains, cattle material and must affirm that the cosmetic was manufactured in accordance with this section. If a cosmetic is manufactured from, processed with, or otherwise contains, cattle material, then the importer of record must, if requested, provide within 5 days records sufficient to demonstrate that the cosmetic is not manufactured from, processed with, or does not otherwise contain, prohibited cattle material.

(7) Records established or maintained to satisfy the requirements of this subpart that meet the definition of electronic records in §11.3(b)(6) of this chapter are exempt from the requirements of part 11 of this chapter. Records that satisfy the requirements of this subpart but that are also required under other applicable statutory provisions or regulations remain subject to part 11 of this chapter.

(d) *Adulteration.* Failure of a manufacturer or processor to operate in compliance with the requirements of paragraph (b) or (c) of this section renders a cosmetic adulterated under section 601(c) of the act.

(e) *Process for designating countries.* A country seeking designation must send a written request to the Director, Office of the Center Director, Center for Food Safety and Applied Nutrition, Food and Drug Administration, at the address designated in 21 CFR 5.1100. The request shall include information about a country's bovine spongiform encephalopathy (BSE) case history, risk factors, measures to prevent the introduction and transmission of BSE, and any other information relevant to determining whether specified risk materials, the small intestine of cattle except as provided in paragraph (b)(2) of this section, material from nonambulatory disabled cattle, or MS (Beef) from cattle from the country should be considered prohibited cattle materials. FDA shall respond in writing to any such request and may impose conditions in granting any such request. A country designation granted by FDA under this paragraph will be subject to future review by FDA, and may be revoked if FDA determines that it is no longer appropriate.

[70 FR 53068, Sept. 7, 2005, as amended at 71 FR 59668, Oct. 11, 2006; 73 FR 20794, Apr. 17, 2008; 81 FR 5596, Feb. 3, 2016; 81 FR 14732, Mar. 18, 2016]

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§700.35 Cosmetics containing sunscreen ingredients.

(a) A product that includes the term “sunscreen” in its labeling or in any other way represents or suggests that it is intended to prevent, cure, treat, or mitigate disease or to affect a structure or function of the body comes within the definition of a drug in section 201(g)(1) of the act. Sunscreen active ingredients affect the structure or function of the body by absorbing, reflecting, or scattering the harmful, burning rays of the sun, thereby altering the normal physiological response to solar radiation. These ingredients also help to prevent diseases such as sunburn and may reduce the chance of premature skin aging, skin cancer, and other harmful effects due to the sun when used in conjunction with limiting sun exposure and wearing protective clothing. When consumers see the term “sunscreen” or similar sun protection terminology in the labeling of a product, they expect the product to protect them in some way from the harmful effects of the sun, irrespective of other labeling statements. Consequently, the use of the term “sunscreen” or similar sun protection terminology in a product's labeling generally causes the product to be subject to regulation as a drug. However, sunscreen ingredients may also be used in some products for nontherapeutic, nonphysiologic uses (e.g., as a color additive or to protect the color of the product). To avoid consumer misunderstanding, if a cosmetic product contains a sunscreen ingredient and uses the term “sunscreen” or similar sun protection terminology anywhere in its labeling, the term must be qualified by describing the cosmetic benefit provided by the sunscreen ingredient.

(b) The qualifying information required under paragraph (a) of this section shall appear prominently and conspicuously at least once in the labeling in conjunction with the term “sunscreen” or other similar sun protection terminology used in the labeling. For example: “Contains a sunscreen—to protect product color.”

[64 FR 27693, May 21, 1999]

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Title 21: Food and Drugs

PART 701—COSMETIC LABELING

Contents

AUTHORITY: 21 U.S.C. 321, 352, 361, 362, 363, 371, 374; 15 U.S.C. 1454, 1455.

SOURCE: 39 FR 10056, Mar. 15, 1974, unless otherwise noted.

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Subpart A—General Provisions

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§701.1 Misbranding.

(a) Among representations in labeling of a cosmetic which render such cosmetic misbranded is a false or misleading representation with respect to another cosmetic or a food, drug, or device.

(b) The labeling of a cosmetic which contains two or more ingredients may be misleading by reason (among other reasons) of the designation of such cosmetic in such labeling by a name which includes or suggests the name of one or more but not all such ingredients, even though the names of all such ingredients are stated elsewhere in the labeling.

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§701.2 Form of stating labeling requirements.

(a) A word, statement, or other information required by or under authority of the Act to appear on the label may lack that prominence and conspicuousness required by section 602(c) of the Act by reason (among other reasons) of:

(1) The failure of such word, statement, or information to appear on the part or panel of the label which is presented or displayed under customary conditions of purchase;

(2) The failure of such word, statement, or information to appear on two or more parts or panels of the label, each of which has sufficient space therefor, and each of which is so designed as to render it likely to be, under customary conditions of purchase, the part or panel displayed;

(3) The failure of the label to extend over the area of the container or package available for such extension, so as to provide sufficient label space for the prominent placing of such word, statement, or information;

(4) Insufficiency of label space (for the prominent placing of such word, statement, or information) resulting from the use of label space for any word, statement, design, or device which is not required by or under authority of the Act to appear on the label;

(5) Insufficiency of label space (for the prominent placing of such word, statement, or information) resulting from the use of label space to give materially greater conspicuousness to any other word, statement, or information, or to any design or device;

(6) Smallness or style of type in which such word, statement, or information appears, insufficient background contrast, obscuring designs or vignettes, or crowding with other written, printed, or graphic matter.

(b)(1) All words, statements, and other information required by or under authority of the Act to appear on the label or labeling shall appear thereon in the English language: *Provided, however,* That in the case of articles distributed solely in the Commonwealth of Puerto Rico or in a Territory where the predominant language is one other than English, the predominant language may be substituted for English.

(2) If the label contains any representation in a foreign language, all words, statements, and other information required by or under authority of the Act to appear on the label shall appear thereon in the foreign language.

(3) If the labeling contains any representation in a foreign language, all words, statements, and other information required by or under authority of the Act to appear on the label or labeling shall appear on the labeling in the foreign language.

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§701.3 Designation of ingredients.

(a) The label on each package of a cosmetic shall bear a declaration of the name of each ingredient in descending order of predominance, except that fragrance or flavor may be listed as fragrance or flavor. An ingredient which is both fragrance and flavor shall be designated by each of the functions it performs unless such ingredient is identified by name. No ingredient may be designated as fragrance or flavor unless it is within the meaning of such term as commonly understood by consumers. Where one or more ingredients is accepted by the Food and Drug Administration as exempt from public disclosure pursuant to the procedure established in §720.8(a) of this chapter, in lieu of label declaration of identity the phrase “and other ingredients” may be used at the end of the ingredient declaration.

(b) The declaration of ingredients shall appear with such prominence and conspicuousness as to render it likely to be read and understood by ordinary individuals under normal conditions of purchase. The declaration shall appear on any appropriate information panel in letters not less than $1/16$ of an inch in height and without obscuring design, vignettes, or crowding. In the absence of sufficient space for such declaration on the package, or where the manufacturer or distributor wishes to use a decorative container, the declaration may appear on a firmly affixed tag, tape, or card. In those cases where there is insufficient space for such declaration on the package, and it is not practical to firmly affix a tag, tape, or card, the Commissioner may establish by regulation an acceptable alternate, e.g., a smaller type size. A petition requesting such a regulation as an amendment to this paragraph shall be submitted pursuant to part 10 of this chapter.

(c) A cosmetic ingredient shall be identified in the declaration of ingredients by:

(1) The name specified in §701.30 as established by the Commissioner for that ingredient for the purpose of cosmetic ingredient labeling pursuant to paragraph (e) of this section;

(2) In the absence of the name specified in §701.30, the name adopted for that ingredient in the following editions and supplements of the following compendia, listed in order as the source to be utilized:

(i) CTFA (Cosmetic, Toiletry and Fragrance Association, Inc.) Cosmetic Ingredient Dictionary, Second Ed., 1977 (available from the Cosmetic, Toiletry and Fragrance Association, Inc. 1110 Vermont Ave. NW., Suite 800, Washington, DC 20005, or at the National Archives and Records Administration (NARA), which is incorporated by reference, except for the following deletions and revisions. (For information on the availability of this material at NARA, call 202-741-6030, or go to: *http://www.archives.gov/federal_register/code_of_federal_regulations/ibr_locations.html.*)

(*a*) The following names are not adopted for the purpose of cosmetic ingredient labeling:

Acid Black 58

Acid Black 107

Acid Black 139

Acid Blue 168

Acid Blue 170

Acid Blue 188

Acid Blue 209

Acid Brown 19

Acid Brown 30

Acid Brown 44

Acid Brown 45

Acid Brown 46

Acid Brown 48

Acid Brown 224

Acid Orange 80

Acid Orange 85

Acid Orange 86

Acid Orange 88

Acid Orange 89

Acid Orange 116

Acid Red 131

Acid Red 213

Acid Red 252

Acid Red 259

Acid Violet 73

Acid Violet 76

Acid Violet 99

Acid Yellow 114

Acid Yellow 127

Direct Yellow 81

Solvent Black 5

Solvent Brown 43

Solvent Yellow 63

Solvent Yellow 90

(*b*) The following names are adopted for the purpose of cosmetic ingredient labeling, provided the respective monographs are revised to describe their otherwise disclosed chemical compositions, or describe their chemical compositions more precisely, and such revised monographs are published in supplements to this dictionary edition by July 18, 1980.

Acid Black 2

Benzophenone-11

Carbomer 934

Carbomer 934P

Carbomer 940

Carbomer 941

Carbomer 960

Carbomer 961

Chlorofluorocarbon 11S

Dimethicone Copolyol

Disperse Red 17

Pigment Green 7

Polyamino Sugar Condensate

SD Alcohol (all 27 alphanumeric designations)

Sodium Chondroitin Sulfate

Synthetic Beeswax

(*c*) The following names are adopted for the purpose of cosmetic ingredient labeling until January 19, 1981.

Amphoteric (all 20 numeric designations)

Quaternium (all 49 numeric designations)

(ii) United States Pharmacopeia, 19th Ed., 1975, and Second Supplement to the USP XIX and NF XIV, 1976. (Copies are available from the U.S. Pharmacopeial Convention, Inc., 12601 Twinbrook Parkway, Rockville, MD 20852, or at the National Archives and Records Administration (NARA). For information on the availability of this material at NARA, call 202-741-6030, or go to: *http://www.archives.gov/federal_register/code_of_federal_regulations/ibr_locations.html.*).

(iii) National Formulary, 14th Ed., 1975, and Second Supplement to the USP XIX and NF XIV, 1976. (Copies are available from the U.S. Pharmacopeial Convention, Inc., 12601 Twinbrook Parkway, Rockville, MD 20852, or at the National Archives and Records Administration (NARA). For information on the availability of this material at NARA, call 202-741-6030, or go to: *http://www.archives.gov/federal_register/code_of_federal_regulations/ibr_locations.html.*).

(iv) Food Chemicals Codex, 2d Ed., 1972; First Supplement, 1974, and Second Supplement, 1975, which are incorporated by reference. Copies are available from the Center for Food Safety and Applied Nutrition, Food and Drug Administration, 5001 Campus Dr., College Park, MD 20740, or at the National Archives and Records Administration (NARA). For information on the availability of this material at NARA, call 202-741-6030, or go to: *http://www.archives.gov/federal_register/code_of_federal_regulations/ibr_locations.html.*

(v) USAN and the USP dictionary of drug names, USAN 1975, 1961-1975 cumulative list. (Copies are available from the U.S. Pharmacopeial Convention, Inc., 12601 Twinbrook Parkway, Rockville, MD 20852, or at the National Archives and Records Administration (NARA). For information on the availability of this material at NARA, call 202-741-6030, or go to: *http://www.archives.gov/federal_register/code_of_federal_regulations/ibr_locations.html.*)

(3) In the absence of such a listing, the name generally recognized by consumers.

(4) In the absence of any of the above, the chemical or other technical name or description.

(d) Where a cosmetic product is also an over-the-counter drug product, the declaration shall declare the active drug ingredients as set forth in §201.66(c)(2) and (d) of this chapter, and the declaration shall declare the cosmetic ingredients as set forth in §201.66(c)(8) and (d) of this chapter.

(e) Interested persons may submit a petition requesting the establishment of a specific name for a cosmetic ingredient pursuant to part 10 of this chapter. The Commissioner may also propose such a name on his own initiative.

(f) As an alternative to listing all ingredients in descending order of predominance, ingredients may be grouped and the groups listed in the following manner and order:

(1) Ingredients, other than color additives, present at a concentration greater than 1 percent, in descending order of predominance; followed by

(2) Ingredients, other than color additives, present at a concentration of not more than 1 percent, without respect to order of predominance; followed by

(3) Color additives, without respect to order of predominance. Ingredients specified in paragraph (f)(2) of this section may be included with those specified in paragraph (f)(1) of this section and listed in descending order of predominance.

(g) A declaration of ingredients may include an ingredient not in the product if the ingredient is identified by the phrase “may contain” and:

(1) It is a color additive added to some batches of the product for purposes of color matching; or

(2)(i) The same declaration of ingredients is also used for other products similar in composition and intended for the same use, including products which may be assortments of products similar in composition and intended for the same use; and

(ii) Such products are “shaded” products, i.e., those falling within the product categories identified in §720.4 (c)(3), (7) and (8)(v) of this chapter; and

(iii) All products sharing the common declaration of ingredients are sold by the labeler under a common trade name or brand designation, and no trade name or brand designation not common to all such products appears in the labeling of any of them; and

(iv) The ingredient is a color additive.

(h) As an alternative to a declaration of color additive ingredients for each product, the color additives of an assortment of cosmetic products that are sold together in the same package may be declared in a single composite list in a manner that is not misleading and that indicates that the list pertains to all the products.

(i) As an alternative to the declaration of ingredients specified in paragraph (b) of this section, the declaration of ingredients may appear in letters not less than $^{1}/_{16}$ of an inch in height in labeling accompanying the product, as for example, on padded sheets or in leaflets, if the total surface area of the package is less than 12 square inches. This paragraph is inapplicable to any packaged cosmetic product enclosed in an outer container, e.g., a folding carton. In addition, this paragraph is applicable only to cosmetic products meeting one of the following requirements:

(1) The cosmetic products are held and displayed for sale in tightly compartmented trays or racks of a display unit. The holder of the labeling bearing the declaration of ingredients shall be attached to the display unit; or

(2) The cosmetic products are “shaded” products, i.e., those falling within the product categories identified in §720.4 (c)(3), (7) and (8)(v) of this chapter, and are held for sale in tightly compartmented trays or racks. The holder of the labeling bearing the declaration of ingredients shall be attached to a display chart bearing samples of the product shades, which is displayed to purchasers. Such a display chart shall be of such construction and design as to permit its continuous use as a display, such as on a counter, and shall be designed for the primary purpose of displaying samples of the shades of the products.

(j) The holder of labeling bearing a declaration of ingredients and used in accordance with paragraph (i) of this section shall be attached to the display unit or chart and shall meet one of the following conditions:

(1) The labeling is on the front of the display unit or chart and can be read in full by a purchaser facing the display unit or chart under customary conditions of retail sale; or

(2) The labeling is on the front of the display unit or chart, is partially visible, and is accompanied by a conspicuous notice on the front of the display unit or chart describing the location of such labeling in letters not less than $^{3}/_{16}$ of an inch in height, e.g., “Ingredient lists above”, that can be read by a purchaser facing the display unit or chart under customary conditions of retail sale, or by the notice required by provisions in paragraph (k)(3) of this section, if conspicuous at all times; or

(3) The labeling is on a side of the display unit or chart, but not on the top, back, or bottom, and is accompanied by a conspicuous notice on the front of the display unit or chart describing the location of such labeling in letters not less than $^{3}/_{16}$ of an inch in height, e.g., “Ingredient lists located on right side of display”, that can be read by a purchaser facing the display unit or chart under customary conditions of retail sale.

(k) Any use of a display unit or chart bearing labeling under the provisions of paragraph (i) of this section shall meet the following requirements:

(1) All articles of labeling bearing ingredient declarations and used in conjunction with any one display unit or chart shall be identical and shall declare the ingredients of all products sold in conjunction with the display unit or chart for which the ingredient declaration is made pursuant to paragraph (i) of this section.

(2) Any display unit or chart intended for such use shall be shipped together with the labeling intended to be attached to it.

(3) Every display unit or chart and/or labeling system shall be designed so that the words “Federal law requires ingredient lists to be displayed here” in letters not less than $^{3}/_{16}$ of an inch in height (i) become conspicuous when no ingredient declarations are displayed and when the last list has been taken, or (ii) are conspicuous at all times adjacent to the place where ingredient declarations are to be attached.

(4) Any labeling containing a declaration of ingredients which reflects a formulation change and not shipped accompanying a display unit or chart shall be dated. Whenever any formulation change is made, and the labeling containing the declaration of ingredients is thereby required to be used in conjunction with products of both the old and new formulations, the labeling shall declare the ingredients of both the old and new formulations separately in a way that is not misleading and in a way that permits the purchaser to identify the ingredient declaration applicable to each package, or which clearly advises the purchaser that the formulation has been changed and that either declaration may be applicable.

(5) Sufficient copies of the declaration of ingredients shall be provided with each shipment of a cosmetic so that a purchaser may obtain a copy of the declaration with each purchase. Display units and replacement labeling for display units shall be accompanied by instructions to the retailer, which when followed will result in compliance with the requirements of this section. Copies of the declaration accompanying refills shall be attached to the specific refill items to which they pertain, or shall be packed with the specific refill items to which they pertain, in a container that does not contain other cosmetic products.

(6) The firm whose name appears on a product pursuant to §701.12 shall promptly mail a copy of the declaration of ingredients to any person requesting it.

(7) The display unit or chart shall be designed and located such that the labeling is easily accessible to a purchaser facing the display unit or chart under customary conditions of retail sale.

(l) The provisions of this section do not require the declaration of incidental ingredients that are present in a cosmetic at insignificant levels and that have no technical or functional effect in the cosmetic. For the purpose of this paragraph, incidental ingredients are:

(1) Substances that have no technical or functional effect in the cosmetic but are present by reason of having been incorporated into the cosmetic as an ingredient of another cosmetic ingredient.

(2) Processing aids, which are as follows:

(i) Substances that are added to a cosmetic during the processing of such cosmetic but are removed from the cosmetic in accordance with good manufacturing practices before it is packaged in its finished form.

(ii) Substances that are added to a cosmetic during processing for their technical or functional effect in the processing, are converted to substances the same as constituents of declared ingredients, and do not significantly increase the concentration of those constituents.

(iii) Substances that are added to a cosmetic during the processing of such cosmetic for their technical and functional effect in the processing but are present in the finished cosmetic at insignificant levels and do not have any technical or functional effect in that cosmetic.

(m) In the event that there is a current or anticipated shortage of a cosmetic ingredient, the declaration required by this section may specify alternatives to any ingredients that may be affected. An alternative ingredient shall be declared either (1) immediately following the normally used ingredient for which it substitutes, in which case it shall be identified as an alternative ingredient by the word “or” following the name of the normally used ingredient and any other alternative ingredient, or (2) following the declaration of all normally used ingredients, in which case the alternative ingredients in the group so listed shall be listed in expected descending order of predominance or in accordance with the provisions of paragraph (f) of this section and shall be identified as alternative ingredients by the phrase “may also contain”. This paragraph is inapplicable to any ingredient mentioned in advertising, or in labeling other than in the declaration of ingredients required by this section.

(n) In the event that the shortage of a cosmetic ingredient necessitates a formulation change, packages bearing labels declaring the ingredients of the old formulation may be used if the revised ingredient declaration appears (1) on a firmly affixed tag, tape, card, or sticker or similar overlabeling attached to the package and bearing the conspicuous words “new ingredient list” in letters not less than $1/16$ of an inch in height, or (2) on labeling inside an unsealed package and the package bears the conspicuous words, on a sticker or similar overlabeling, “new ingredient list inside” in letters not less than $1/16$ of an inch in height.

(o) The ingredients of products that are similar in composition and intended for the same use may be declared as follows:

(1) The declaration of ingredients for an assortment of such products that are sold together in the same package, e.g., eyeshadows of different colors, may declare the ingredients that are common to all the products, in a single list in their cumulative order of predominance or in accordance with the provisions of paragraph (f) of this section, together with a statement, in terms that are as informative as practicable and that are not misleading, declaring the other ingredients and identifying the products in which they are present. The color additive ingredients of all the products in such an assortment, whether or not common to all the products, may be declared in a single composite list following the declaration of the other ingredients without identifying the products in which they are present.

(2) The ingredients of an assortment of such products that are sold together in the same package, e.g., eyeshadows of different colors, may be declared in a single list in their cumulative order of predominance or in accordance with the provisions of paragraph (f) of this section, if the package is designed such that it has a total surface area available to bear labeling of less than 12 square inches. For the purpose of this paragraph, surface area is not available for labeling if physical characteristics of the package surface, e.g., decorative relief, make application of a label impractical.

(3) The declaration of ingredients for such a product that is individually packaged and bears a label that is shared with other products pursuant to the provisions of paragraph (g)(2) of this section, e.g., one lipstick in a line of lipsticks, may declare the ingredients that are common to all such products, in a single list in their cumulative order of predominance or in accordance with the provisions of paragraph (f) of this section, together with a statement, in terms that are as informative as practicable and that are not misleading, declaring the other ingredients in such products, and identifying the products in which they are present. The color additive ingredients shall be declared in accordance with the provisions of paragraph (g) of this section.

(4) The declaration of ingredients for an assortment of such cosmetic products that bears a label that is shared with other products pursuant to the provisions of paragraph (g)(2) of this section, e.g., one of several compacts in a line of compacts, may declare the ingredients that are common to all such products, in a single list in their cumulative order of predominance or in accordance with the provisions of paragraph (f) of this section, together with a statement, in terms that are as informative as practicable and that are not misleading, declaring the other ingredients in such products and identifying the products in which they are present. The color additive ingredients shall be declared in accordance with the provisions of paragraph (g) of this section.

(p) As an alternative to the declaration of ingredients in letters not less than $1/16$ of an inch in height, letters may be not less than $1/32$ of an inch in height if the package is designed such that it has a total surface area available to bear labeling of less than 12 square inches. For the purpose of this paragraph, surface area is not available for labeling if physical characteristics of the package surface, e.g., decorative relief, make application of a label impractical.

(q) The inside containers in a multiunit or multicomponent retail cosmetic package are not required to bear a declaration of ingredients when the labeling of the multiunit or multicomponent retail cosmetic package meets all the requirements of this section and the inside containers are not intended to be, and are not customarily, separated from the retail package for retail sale.

(r) In the case of cosmetics distributed to the consumers by direct mail, as an alternative to the declaration of ingredients on an information panel, the declaration of ingredients may appear in letters not less than $1/16$ of an inch in height in labeling that accompanies and specifically relates to the cosmetic(s) mailed, or in labeling furnished to each consumer for his personal use and from which he orders cosmetics through the mail, e.g., a direct mail sales catalog or brochure, provided all of the following additional requirements are met:

(1) The declarations of ingredients are conspicuous and presented in a way that permits the consumer to identify the declaration of ingredients applicable to each cosmetic.

(2) The package mailed to the consumer is accompanied by a notice located on, or affixed to, the top of the package or on top of the contents inside the package, or on the face of the package platform surrounding and holding the product(s), readily visible to the consumer on opening of the package, and provides the following information in letters not less than $3/16$ of an inch in height:

(i) The location of the declarations of ingredients, e.g., in an accompanying brochure, or in a sales catalog used for ordering;

(ii) A statement that a copy of the declaration of ingredients will be mailed promptly to any person requesting it; and

(iii) The name and place of business of the mail order distributor,

(3) The mail order distributor promptly mails a copy of the declaration of ingredients to any person requesting it.

[39 FR 10056, Mar. 15, 1974, as amended at 40 FR 8922, Mar. 3, 1975; 40 FR 18426, Apr. 28, 1975; 42 FR 4718, Jan. 25, 1977; 42 FR 15676, Mar. 22, 1977; 42 FR 24255, May 31, 1977; 42 FR 46516, Sept. 16, 1977; 42 FR 61257, Dec. 2, 1977; 45 FR 3577, Jan. 18, 1980; 47 FR 9397, Mar. 5, 1982; 54 FR 24900, June 12, 1989; 64 FR 13297, Mar. 17, 1999; 69 FR 18803, Apr. 9, 2004; 81 FR 49897, July 29, 2016]

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§701.9 Exemptions from labeling requirements.

(a) Except as provided by paragraphs (b) and (c) of this section, a shipment or other delivery of a cosmetic which is, in accordance with the practice of the trade, to be processed, labeled, or repacked in substantial quantity at an establishment other than that where originally processed or packed, shall be exempt, during the time of introduction into and movement in interstate commerce and the time of holding in such establishment, from compliance with the labeling requirements of sections 601(a) and 602(b) of the act if:

(1) The person who introduced such shipment or delivery into interstate commerce is the operator of the establishment where such cosmetic is to be processed, labeled, or repacked; or

(2) In case such person is not such operator, such shipment or delivery is made to such establishment under a written agreement, signed by and containing the post office addresses of such person and such operator, and containing such specifications for the processing, labeling, or repacking, as the case may be, of such cosmetic in such establishment as will insure, if such specifications are followed, that such cosmetic will not be adulterated or misbranded within the meaning of the act upon completion of such processing, labeling, or repacking. Such person and such operator shall each keep a copy of such agreement until 2 years after the final shipment or delivery of such cosmetic from such establishment, and shall make such copies available for inspection at any reasonable hour to any officer or employee of the Department who requests them.

(b) An exemption of a shipment or other delivery of a cosmetic under paragraph (a)(1) of this section shall, at the beginning of the act of removing such shipment or delivery, or any part thereof, from such establishment, become void ab initio if the cosmetic comprising such shipment, delivery, or part is adulterated or misbranded within the meaning of the act when so removed.

(c) An exemption of a shipment or other delivery of a cosmetic under paragraph (a)(2) of this section shall become void ab initio with respect to the person who introduced such shipment or delivery into interstate commerce upon refusal by such person to make available for inspection a copy of the agreement, as required by such clause.

(d) An exemption of a shipment or other delivery of a cosmetic under paragraph (a)(2) of this section shall expire:

(1) At the beginning of the act of removing such shipment or delivery, or any part thereof, from such establishment if the cosmetic comprising such shipment, delivery, or part is adulterated or misbranded within the meaning of the act when so removed; or

(2) Upon refusal by the operator of the establishment where such cosmetic is to be processed, labeled, or repacked, to make available for inspection a copy of the agreement, as required by such clause.

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Subpart B—Package Form

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§701.10 Principal display panel.

The term *principal display panel* as it applies to cosmetics in package form and as used in this part, means the part of a label that is most likely to be displayed, presented, shown, or examined under customary conditions of display for retail sale. The principal display panel shall be large enough to accommodate all the mandatory label information required to be placed thereon by this part with clarity and conspicuousness and without obscuring designs, vignettes, or crowding. Where packages bear alternate principal display panels, information required to be placed on the principal display panel shall be duplicated on each principal display panel. For the purpose of obtaining uniform type size in declaring the quantity of contents of all packages of substantially the same size, the term “area of the principal display panel” means the area of the side or surface that bears the principal display panel, which area shall be:

(a) In the case of a rectangular package where one entire side properly can be considered to be the principal display panel side, the product of the height times the width of that side;

(b) In the case of a cylindrical or nearly cylindrical container, 40 percent of the product of the height of the container times the circumference; and

(c) In the case of any other shape of container, 40 percent of the total surface of the container: *Provided, however,* That where such container presents an obvious “principal display panel” such as the top of a triangular or circular package, the area shall consist of the entire top surface.

In determining the area of the principal display panel, exclude tops, bottoms, flanges at the tops and bottoms of cans, and shoulders and necks of bottles or jars. In the case of cylindrical or nearly cylindrical containers, information required by this part to appear on the principal display panel shall appear within that 40 percent of the circumference which is most likely to be displayed, presented, shown, or examined under customary conditions of display for retail sale.

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§701.11 Identity labeling.

(a) The principal display panel of a cosmetic in package form shall bear as one of its principal features a statement of the identity of the commodity.

(b) Such statement of identity shall be in terms of:

(1) The common or usual name of the cosmetic; or

(2) An appropriately descriptive name or, when the nature of the cosmetic is obvious, a fanciful name understood by the public to identify such cosmetic; or

(3) An appropriate illustration or vignette representing the intended cosmetic use.

(c) The statement of identity shall be presented in bold type on the principal display panel, shall be in a size reasonably related to the most prominent printed matter on such panel, and shall be in lines generally parallel to the base on which the package rests as it is designed to be displayed.

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§701.12 Name and place of business of manufacturer, packer, or distributor.

(a) The label of a cosmetic in package form shall specify conspicuously the name and place of business of the manufacturer, packer, or distributor.

(b) The requirement for declaration of the name of the manufacturer, packer, or distributor shall be deemed to be satisfied in the case of a corporation only by the actual corporate name, which may be preceded or followed by the name of the particular division of the corporation. Abbreviations for “Company,” “Incorporated,” etc., may be used and “The” may be omitted. In the case of an individual, partnership, or association, the name under which the business is conducted shall be used.

(c) Where the cosmetic is not manufactured by the person whose name appears on the label, the name shall be qualified by a phrase that reveals the connection such person has with such cosmetic; such as, “Manufactured for _____”, “Distributed by _____”, or any other wording that expresses the facts.

(d) The statement of the place of business shall include the street address, city, State, and ZIP Code; however, the street address may be omitted if it is shown in a current city directory or telephone directory. The requirement for inclusion of the ZIP Code shall apply only to consumer commodity labels developed or revised after the effective date of this section. In the case of nonconsumer packages, the ZIP Code shall appear either on the label or the labeling (including the invoice).

(e) If a person manufactures, packs, or distributes a cosmetic at a place other than his principal place of business, the label may state the principal place of business in lieu of the actual place where such cosmetic was manufactured or packed or is to be distributed, unless such statement would be misleading.

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§701.13 Declaration of net quantity of contents.

(a) The label of a cosmetic in package form shall bear a declaration of the net quantity of contents. This shall be expressed in terms of weight, measure, numerical count, or a combination of numerical count and weight or measure. The statement shall be in terms of fluid measure if the cosmetic is liquid or in terms of weight if the cosmetic is solid, semisolid, or viscous, or a mixture of solid and liquid. If there is a firmly established, general consumer usage and trade custom of declaring the net quantity of a cosmetic by numerical count, linear measure, or measure of area, such respective term may be used. If there is a firmly established, general consumer usage and trade custom of declaring the contents of a liquid cosmetic by weight, or a solid, semisolid, or viscous cosmetic by fluid measure, it may be used. Whenever the Commissioner determines for a specific packaged cosmetic that an existing practice of declaring net quantity of contents by weight, measure, numerical count, or a combination of these does not facilitate value comparisons by consumers, he shall by regulation designate the appropriate term or terms to be used for such cosmetic.

(b) Statements of weight shall be in terms of avoirdupois pound and ounce. Statements of fluid measure shall be in terms of the U.S. gallon of 231 cubic inches and quart, pint, and fluid-ounce subdivisions thereof and shall express the volume at 68 °F. (20 °C.).

(c) When the declaration of quantity of contents by numerical count, linear measure, or measure of area does not give accurate information as to the quantity of cosmetic in the package, it shall be augmented by such statement of weight, measure, or size of the individual units or the total weight or measure of the cosmetic as will give such information.

(d) The declaration may contain common or decimal fractions. A common fraction shall be in terms of halves, quarters, eighths, sixteenths, or thirty-seconds; except that if there exists a firmly established, general consumer usage and trade custom of employing different common fractions in the net quantity declaration of a particular commodity they may be employed. A common fraction shall be reduced to its lowest terms; a decimal fraction shall not be carried out to more than two places. A

statement that includes small fractions of an ounce shall be deemed to permit smaller variations than one which does not include such fractions.

(e) The declaration shall be located on the principal display panel of the label; with respect to packages bearing alternate principal display panels, it shall be duplicated on each principal display panel: *Provided,* That:

(1) The principal display panel of a cosmetic marketed in a “boudoir-type” container including decorative cosmetic containers of the “cartridge,” “pill box,” “compact,” or “pencil” variety, and those with a capacity of one-fourth ounce or less, may be considered to be a tear-away tag or tape affixed to the decorative container and bearing the mandatory label information as required by this part, but the type size of the net quantity of contents statement shall be governed by the dimensions of the decorative container; and

(2) The principal display panel of a cosmetic marketed on a display card to which the immediate container is affixed may be considered to be the display panel of the card, and the type size of the net quantity of content statement is governed by the dimensions of the display card.

(f) The declaration shall appear as a distinct item on the principal display panel, shall be separated (by at least a space equal to the height of the lettering used in the declaration) from other printed label information appearing above or below the declaration and (by at least a space equal to twice the width of the letter “N” of the style of type used in the quantity of contents statement) from other printed label information appearing to the left or right of the declaration. It shall not include any term qualifying a unit of weight, measure, or count (such as “giant pint” and “full quart”) that tends to exaggerate the amount of the cosmetic in the container. It shall be placed on the principal display panel within the bottom 30 percent of the area of the label panel in line generally parallel to the base on which the package rests as it is designed to be displayed: *Provided,* That:

(1) On packages having a principal display panel of 5 square inches or less, the requirement for placement within the bottom 30 percent of the area of the label panel shall not apply when the declaration of net quantity of contents meets the other requirements of this part; and

(2) In the case of a cosmetic that is marketed with both outer and inner retail containers bearing the mandatory label information required by this part, and the inner container is not intended to be sold separately, the net quantity of contents placement requirement of this section applicable to such inner containers is waived.

(g) The declaration shall accurately reveal the quantity of cosmetic in the package exclusive of wrappers and other material packed therewith: *Provided,* That:

(1) In the case of cosmetics packed in containers designed to deliver the cosmetic under pressure, the declaration shall state the net quantity of the contents that will be expelled when the instructions for use as shown on the container are followed. The propellant is included in the net quantity declaration; and

(2) In the case of a package which contains the integral components making up a complete kit, and which is designed to deliver the components in the manner of an application (for example, a home permanent wave kit), the declaration may state the net quantity of the contents in nondeceptive terms of the number of applications available in the kit when the instructions for use as shown on the container are followed.

(h) The declaration shall appear in conspicuous and easily legible boldface print or type in distinct contrast (by typography, layout, color, embossing, or molding) to other matter on the package; except that a declaration of net quantity blown, embossed, or molded on a glass or plastic surface is permissible when all label information is so formed on the surface. Requirements of conspicuousness and legibility shall include the specifications that:

(1) The ratio of height to width (of the letter) shall not exceed a differential of 3 units to 1 unit (no more than 3 times as high as it is wide).

(2) Letter heights pertain to upper case or capital letters. When upper and lower case or all lower case letters are used, it is the lower case letter “o” or its equivalent that shall meet the minimum standards.

(3) When fractions are used, each component numeral shall meet one-half the minimum height standards.

(i) The declaration shall be in letters and numerals in a type size established in relationship to the area of the principal display panel of the package and shall be uniform for all packages of substantially the same size by complying with the following type specifications:

(1) Not less than one-sixteenth inch in height on packages the principal display panel of which has an area of 5 square inches or less.

(2) Not less than one-eighth inch in height on packages the principal display panel of which has an area of more than 5 but not more than 25 square inches.

(3) Not less than three-sixteenths inch in height on packages the principal display panel of which has an area of more than 25 but not more than 100 square inches.

(4) Not less than one-fourth inch in height on packages the principal display panel of which has an area of more than 100 square inches, except not less than one-half inch in height if the area is more than 400 square inches.

Where the declaration is blown, embossed, or molded on a glass or plastic surface rather than by printing, typing, or coloring, the lettering sizes specified in paragraphs (i)(1) through (4) of this section shall be increased by one-sixteenth of an inch.

(j) On packages containing less than 4 pounds or 1 gallon and labeled in terms of weight or fluid measure:

(1) The declaration shall be expressed both in ounces, with identification by weight or by liquid measure and, if applicable (1 pound or 1 pint or more), followed in parentheses by a declaration in pounds for weight units, with any remainder in terms of ounces or common or decimal fractions of the pound (as set forth in paragraphs (m)(1) and (2) of this section), or in the case of liquid measure, in the largest whole units (quarts, quarts and pints, or pints, as appropriate) with any remainder in terms of fluid ounces or common or decimal fractions of the pint or quart (as set forth in paragraphs (m)(3) and (4) of this section). Net weight or fluid measure of less than 1 ounce shall be expressed in common or decimal fractions of the respective ounce and not in drams.

(2) The declaration may appear in more than one line. The term “net weight” shall be used when stating the net quantity of contents in terms of weight. Use of the terms “net” or “net contents” in terms of fluid measure or numerical count is optional. It is sufficient to distinguish avoirdupois ounce from fluid ounce through association of terms; for example, “Net wt. 6 oz.” or “6 oz. net wt.” and “Net contents 6 fl. oz.” or “6 fl. oz.”

(k) On packages containing 4 pounds or 1 gallon or more and labeled in terms of weight or fluid measure, the declaration shall be expressed in pounds for weight units with any remainder in terms of ounces or common or decimal fractions of the pound; in the case of fluid measure, it shall be expressed in the largest whole unit (gallons, followed by common or decimal fractions of a gallon or by the next smaller whole unit or units (quarts or quarts and pints)) with any remainder in terms of fluid ounces or common or decimal fractions of the pint or quart (as set forth in paragraph (m)(5) of this section).

(l) [Reserved]

(m) Examples: (1) A declaration of 1½ pounds weight shall be expressed as “Net wt. 24 oz. (1 lb. 8 oz.)”, “Net wt. 24 oz. (1½ lb.)”, or “Net wt. 24 oz. (1.5 lb.)”.

(2) A declaration of three-fourths pound avoirdupois weight shall be expressed as “Net wt. 12 oz.”

(3) A declaration of 1 quart liquid measure shall be expressed as “Net contents 32 fl. oz. (1 qt.)”.

(4) A declaration of 1¾ quarts liquid measure shall be expressed as “Net contents 56 fl. oz. (1 qt. 1½ pt.)” or “Net contents 56 fl. oz. (1 qt. 1 pt. 8 oz.)” but not in terms of quart and ounce such as “Net content 56 fl. oz. (1 qt. 24 oz.)”.

(5) A declaration of 2½ gallons liquid measure shall be expressed in the alternative as “Net contents 2 gal. 2 qt.” and not as “2 gal. 4 pt.”

(n) For quantities, the following abbreviations and none other may be employed (periods and plural forms are optional):

weight wt.	gallon gal.
square sq.	quart qt.
fluid fl.	pint pt.
yard yd.	ounce oz.
feet or foot ft.	pound lb.
inch in.	

(o) On packages labeled in terms of linear measure, the declaration shall be expressed both in terms of inches and, if applicable (1 foot or more), the largest whole units (yards, yards and feet, feet). The declaration in terms of the largest whole units shall be in parentheses following the declaration in terms of inches and any remainder shall be in terms of inches or common or decimal fractions of the foot or yard. Examples are “86 inches (2 yd. 1 ft. 2 inches)”, “90 inches (2½ yd.)”, “30 inches (2.5 ft.)”, etc.

(p) On packages labeled in terms of area measure, the declaration shall be expressed in terms of square inches and, if applicable (1 square foot or more), the largest whole square unit (square yards, square yards and square feet, square feet). The

declaration in terms of the largest whole units shall be in parentheses following the declaration in terms of square inches and any remainder shall be in terms of square inches or common or decimal fractions of the square foot or square yard; for example, “158 sq. inches (1 sq. ft. 14 sq. inches)”, etc.

(q) Nothing in this section shall prohibit supplemental statements at locations other than the principal display panel(s) describing in nondeceptive terms the net quantity of contents, provided that such supplemental statements of net quantity of contents shall not include any term qualifying a unit of weight, measure, or count that tends to exaggerate the amount of the cosmetic contained in the package; for example, “giant pint” and “full quart.” Dual or combination declarations of net quantity of contents as provided for in paragraphs (a), (c), and (j) of this section (for example, a combination of net weight plus numerical count) are not regarded as supplemental net quantity statements and shall be located on the principal display panel.

(r) A separate statement of the net quantity of contents in terms of the metric system is not regarded as a supplemental statement and an accurate statement of the net quantity of contents in terms of the metric system of weight or measure may also appear on the principal display panel or on other panels.

(s) The declaration of net quantity of contents shall express an accurate statement of the quantity of contents of the package. Reasonable variations caused by loss or gain of moisture during the course of good distribution practice or by unavoidable deviations in good manufacturing practice will be recognized. Variations from stated quantity of contents shall not be unreasonably large.

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Subpart C—Labeling of Specific Ingredients

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§701.20 Detergent substances, other than soap, intended for use in cleansing the body.

(a) In its definition of the term *cosmetic,* the Federal Food, Drug, and Cosmetic Act specifically excludes soap. The term *soap* is nowhere defined in the act. In administering the act, the Food and Drug Administration interprets the term “soap” to apply only to articles that meet the following conditions:

(1) The bulk of the nonvolatile matter in the product consists of an alkali salt of fatty acids and the detergent properties of the article are due to the alkali-fatty acid compounds; and

(2) The product is labeled, sold, and represented only as soap.

(b) Products intended for cleansing the human body and which are not “soap” as set out in paragraph (a) of this section are “cosmetics,” and accordingly they are subject to the requirements of the act and the regulations thereunder. For example, such a product in bar form is subject to the requirement, among others, that it shall bear a label containing an accurate statement of the weight of the bar in avoirdupois pounds and ounces, this statement to be prominently and conspicuously displayed so as to be likely to be read under the customary conditions of purchase and use.

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§701.30 Ingredient names established for cosmetic ingredient labeling.

The Commissioner establishes the following names for the purpose of cosmetic ingredient labeling pursuant to paragraph (e) of §701.3:

Chemical name or description	Chemical formula	Established label name
Trichlorofluoromethane	CCl_3F	Chlorofluorocarbon 11.
Trichlorofluoromethane and 0.3 pct nitromethane	$CCl_3F + CH_3NO_2$	Chlorofluorocarbon 11 S.
Dichlorodifluoromethane	CCl_2F_2	Chlorofluorocarbon 12.
Chlorodifluoromethane	$CHClF_2$	Hydrochlorofluorocarbon 22.
1, 2-dichloro-1, 1, 2, 2-tetrafluoroethane	$CClF_2CClF_2$	Chlorofluorocarbon 114.
1-Chloro-1, 1-difluoroethane	CH_3CClF_2	Hydrochlorofluorocarbon 142 B.
1, 1-difluoroethane	CH_3CHF_2	Hydrofluorocarbon 152 A.
Ethyl ester of hydrolyzed animal protein is the ester of ethyl alcohol and the hydrolysate of collagen or other animal protein, derived by acid, enzyme, or other form of hydrolysis		Ethyl ester of hydrolyzed animal protein.

[42 FR 24255, May 13, 1977, as amended at 45 FR 3577, Jan. 18, 1980]

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Need assistance?

Title 21: Food and Drugs

PART 720—VOLUNTARY FILING OF COSMETIC PRODUCT INGREDIENT COMPOSITION STATEMENTS

Contents

AUTHORITY: 21 U.S.C. 321, 331, 361, 362, 371, 374.

SOURCE: 39 FR 10060, Mar. 15, 1974, unless otherwise noted.

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§720.1 Who should file.

Either the manufacturer, packer, or distributor of a cosmetic product is requested to file Form FDA 2512 (“Cosmetic Product Ingredient Statement”), whether or not the cosmetic product enters interstate commerce. This request extends to any foreign manufacturer, packer, or distributor of a cosmetic product exported for sale in any State as defined in section 201(a)(1) of the Federal Food, Drug, and Cosmetic Act. No filing fee is required.

[57 FR 3129, Jan. 28, 1992]

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§720.2 Times for filing.

Within 180 days after forms are made available to the industry, Form FDA 2512 should be filed for each cosmetic product being commercially distributed as of the effective date of this part. Form FDA 2512 should be filed within 60 days after the beginning of commercial distribution of any product not covered within the 180-day period.

[57 FR 3129, Jan. 28, 1992]

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§720.3 How and where to file.

Forms FDA 2512 and FDA 2514 (“Discontinuance of Commercial Distribution of Cosmetic Product Formulation”) are obtainable on request from the Food and Drug Administration, 5001 Campus Dr., College Park, MD 20740, or at any Food and Drug Administration district office. The completed form should be mailed or delivered to: Cosmetic Product Statement, Food and Drug Administration, 5001 Campus Dr., College Park, MD 20740, according to the instructions provided with the forms.

[57 FR 3129, Jan. 28, 1992, as amended at 68 FR 15355, Mar. 31, 2003; 81 FR 49897, July 29, 2016]

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§720.4 Information requested about cosmetic products.

(a) Form FDA-2512 requests information on:

(1) The name and address, including post office ZIP code of the person (manufacturer, packer, or distributor) designated on the label of the product.

(2) The name and address, including post office ZIP code, of the manufacturer or packer of the product if different from the person designated on the label of the product, when the manufacturer or packer submits the information requested under this paragraph.

(3) The brand name or names of the cosmetic product.

(4) The cosmetic product category or categories.

(5) The ingredients in the product.

(b) The person filing Form FDA-2512 should:

(1) Provide the information requested in paragraph (a) of this section.

(2) Have the form signed by an authorized individual.

(3) Provide poison control centers with ingredient information and/or adequate diagnostic and therapeutic procedures to permit rapid evaluation and treatment of accidental ingestion or other accidental use of the cosmetic product.

(4) Provide ingredient information (and, when requested, ingredient samples) to a licensed physician who, in connection with the treatment of a patient, requests assistance in determining whether an ingredient in the cosmetic product is the cause of the problem for which the patient is being treated.

(c) One or more of the following cosmetic product categories should be cited to indicate the product's intended use.

(1) *Baby products.* (i) Baby shampoos.

(ii) Lotions, oils, powders, and creams.

(iii) Other baby products.

(2) *Bath preparations.* (i) Bath oils, tablets, and salts.

(ii) Bubble baths.

(iii) Bath capsules.

(iv) Other bath preparations.

(3) *Eye makeup preparations.* (i) Eyebrow pencil.

(ii) Eyeliner.

(iii) Eye shadow.

(iv) Eye lotion.

(v) Eye makeup remover.

(vi) Mascara.

(vii) Other eye makeup preparations.

(4) *Fragrance preparations.* (i) Colognes and toilet waters.

(ii) Perfumes.

(iii) Powders (dusting and talcum) (excluding aftershave talc).

(iv) Sachets.

(v) Other fragrance preparations.

(5) *Hair preparations (noncoloring).* (i) Hair conditioners.

(ii) Hair sprays (aerosol fixatives).

(iii) Hair straighteners.

(iv) Permanent waves.

(v) Rinses (noncoloring).

(vi) Shampoos (noncoloring).

(vii) Tonics, dressings, and other hair grooming aids.

(viii) Wave sets.

(ix) Other hair preparations.

(6) *Hair coloring preparations.* (i) Hair dyes and colors (all types requiring caution statement and patch test).

(ii) Hair tints.

(iii) Hair rinses (coloring).

(iv) Hair shampoos (coloring).

(v) Hair color sprays (aerosol).

(vi) Hair lighteners with color.

(vii) Hair bleaches.

(viii) Other hair coloring preparations.

(7) *Makeup preparations (not eye).* (i) Blushers (all types).

(ii) Face powders.

(iii) Foundations.

(iv) Leg and body paints.

(v) Lipstick.

(vi) Makeup bases.

(vii) Rouges.

(viii) Makeup fixatives.

(ix) Other makeup preparations.

(8) *Manicuring preparations.* (i) Basecoats and undercoats.

(ii) Cuticle softeners.

(iii) Nail creams and lotions.

(iv) Nail extenders.

(v) Nail polish and enamel.

(vi) Nail polish and enamel removers.

(vii) Other manicuring preparations.

(9) *Oral hygiene products.* (i) Dentifrices (aerosol, liquid, pastes, and powders).

(ii) Mouthwashes and breath fresheners (liquids and sprays).

(iii) Other oral hygiene products.

(10) *Personal cleanliness.* (i) Bath soaps and detergents.

(ii) Deodorants (underarm).

(iii) Douches.

(iv) Feminine hygiene deodorants.

(v) Other personal cleanliness products.

(11) *Shaving preparations.* (i) Aftershave lotions.

(ii) Beard softeners.

(iii) Men's talcum.

(iv) Preshave lotions (all types).

(v) Shaving cream (aerosol, brushless, and lather).

(vi) Shaving soap (cakes, sticks, etc.).

(vii) Other shaving preparation products.

(12) *Skin care preparations, (creams, lotions, powder, and sprays).* (i) Cleansing (cold creams, cleansing lotions, liquids, and pads).

(ii) Depilatories.

(iii) Face and neck (excluding shaving preparations).

(iv) Body and hand (excluding shaving preparations).

(v) Foot powders and sprays.

(vi) Moisturizing.

(vii) Night.

(viii) Paste masks (mud packs).

(ix) Skin fresheners.

(x) Other skin care preparations.

(13) *Suntan preparations.* (i) Suntan gels, creams, and liquids.

(ii) Indoor tanning preparations.

(iii) Other suntan preparations.

(d) Ingredients in the product should be listed as follows:

(1) A list of each ingredient of the cosmetic product in descending order of predominance by weight (except that the fragrance and/or flavor may be designated as such without naming each individual ingredient when the manufacturer or supplier of the fragrance and/or flavor refuses to disclose ingredient data).

(2) An ingredient should be listed by the name adopted by the Food and Drug Administration (FDA) for the ingredient pursuant to §701.3(c) of this chapter.

(3) In the absence of a name adopted by FDA pursuant to §701.3(c) of this chapter, its common or usual name, if it has one, or its chemical or technical name should be listed.

(4) If an ingredient is a mixture, each ingredient of the mixture should be listed in accordance with paragraphs (d)(2) and (d)(3) of this section, unless such mixture is a formulation voluntarily registered on Form FDA 2512, in which case such mixture

should be identified as “fragrance,” “flavor,” “fragrance and flavor” or “base formulation,” as appropriate, and by stating its FDA-assigned cosmetic product ingredient statement number.

(5) When the manufacturer or supplier of a fragrance and/or flavor refuses to disclose ingredient data, the fragrance and/or flavor should be listed as such. The nonconfidential listing of the product name and/or trade name or name of the manufacturer or supplier of each proprietary fragrance and/or flavor mixture is optional.

(e) A separate Form FDA-2512 should be filed for each different formulation of a cosmetic product. However, except for the hair coloring preparations listed in paragraph (c)(6) of this section for which a statement for each shade of such product is required, a single Form FDA-2512 may be filed for two or more shades of a cosmetic product where only the amounts of the color additive ingredient used are varied or in the case of flavors and fragrances where only the amounts of the flavors and fragrances used are varied.

(Information collection requirements in this section were approved by the Office of Management and Budget (OMB) and assigned OMB control number 0910-0030)

[39 FR 10060, Mar. 15, 1974, as amended at 46 FR 38073, July 24, 1981; 57 FR 3129, Jan. 28, 1992]

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§720.6 Amendments to statement.

Changes in the information requested under §§720.4 (a)(3) and (a)(5) on the ingredients or brand name of a cosmetic product should be submitted by filing an amended Form FDA 2512 within 60 days after the product is entered into commercial distribution. Other changes do not justify immediate amendment, but should be shown by filing an amended Form FDA 2512 within a year after such changes. Notice of discontinuance of commercial distribution of a cosmetic product formulation should be submitted by Form FDA 2514 within 180 days after discontinuance of commercial distribution becomes known to the person filing.

[57 FR 3130, Jan. 28, 1992, as amended at 67 FR 9587, Mar. 4, 2002]

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§720.7 Notification of person submitting cosmetic product ingredient statement.

When Form FDA 2512 is received, FDA will either assign a permanent cosmetic product ingredient statement number or a Food and Drug Administration (FDA) reference number in those cases where a permanent number cannot be assigned. Receipt of the form will be acknowledged by sending the individual signing the statement an appropriate notice bearing either the FDA reference number or the permanent cosmetic product ingredient statement number. If the person submitting Form FDA 2512 has not complied with §§720.4 (b)(1) and (b)(2), the person will be notified as to the manner in which the statement is incomplete.

[57 FR 3130, Jan. 28, 1992]

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§720.8 Confidentiality of statements.

(a) Data and information contained in, attached to, or included with Forms FDA 2512 and FDA 2514, and amendments thereto are submitted voluntarily to the Food and Drug Administration (FDA). Any request for confidentiality of a cosmetic ingredient submitted with such forms or separately will be handled in accordance with the procedure set forth in this section. The request for confidentiality will also be subject to the provisions of §20.111 of this chapter, as well as to the exemptions in subpart D of part 20 of this chapter and to the limitations on exemption in subpart E of part 20 of this chapter.

(b) Any request for confidentiality of the identity of a cosmetic ingredient should contain a full statement, in a well-organized format, of the factual and legal grounds for that request, including all data and other information on which the petitioner relies, as well as representative information known to the petitioner that is unfavorable to the petitioner's position. The statement of the factual grounds should include, but should not be limited to, scientific or technical data, reports, tests, and other relevant information addressing the following factors that FDA will consider in determining whether the identity of an ingredient qualifies as a trade secret:

(1) The extent to which the identity of the ingredient is known outside petitioner's business;

(2) The extent to which the identity of the ingredient is known by employees and others involved in petitioner's business;

(3) The extent of measures taken by the petitioner to guard the secrecy of the information;

(4) The value of the information about the identity of the claimed trade secret ingredient to the petitioner and to its competitors;

(5) The amount of effort or money expended by petitioner in developing the ingredient; and

(6) The ease or difficulty with which the identity of the ingredient could be properly acquired or duplicated by others.

(c) The request for confidentiality should also be accompanied by a statement that the identity of the ingredient for which confidentiality is requested has not previously been published or disclosed to anyone other than as provided in §20.81(a) of this chapter.

(d) FDA will return to the petitioner any request for confidentiality that contains insufficient data to permit a review of the merits of the request. FDA will also advise the petitioner about the additional information that is necessary to enable the agency to proceed with its review of the request.

(e) If, after receiving all of the data that are necessary to make a determination about whether the identity of an ingredient is a trade secret, FDA tentatively decides to deny the request, the agency will inform the person requesting trade secrecy of its tentative determination in writing. FDA will set forth the grounds upon which it relied in making this tentative determination. The petitioner may withdraw the records for which FDA has tentatively denied a request for confidentiality or may submit, within 60 days from the date of receipt of the written notice of the tentative denial, additional relevant information and arguments and request that the agency reconsider its decision in light of both the additional material and the information that it originally submitted.

(f) If the petitioner submits new data in response to FDA's tentative denial of trade secret status, the agency will consider that material together with the information that was submitted initially before making its final determination.

(g) A final determination that an ingredient is not a trade secret within the meaning of §20.61 of this chapter constitutes final agency action that is subject to judicial review under 5 U.S.C. Chapter 7. If suit is brought within 30 calendar days after such a determination, FDA will not disclose the records involved or require that the disputed ingredient or ingredients be disclosed in labeling until the matter is finally determined in the courts. If suit is not brought within 30 calendar days after a final determination that an ingredient is not a trade secret within the meaning of 21 CFR 20.61, and the petitioner does not withdraw the records for which a request for confidentiality has been denied, the records involved will be made a part of FDA files and will be available for public disclosure upon request.

[51 FR 11444, Apr. 3, 1986, as amended at 57 FR 3130, Jan. 28, 1992; 68 FR 25288, May 12, 2003]

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§720.9 Misbranding by reference to filing or to statement number.

The filing of Form FDA 2512 or assignment of a number to the statement does not in any way denote approval by the Food and Drug Administration of the firm or the product. Any representation in labeling or advertising that creates an impression of official approval because of such filing or such number will be considered misleading.

[57 FR 3130, Jan. 28, 1992]

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Title 21: Food and Drugs

PART 740—COSMETIC PRODUCT WARNING STATEMENTS

Contents

AUTHORITY: 21 U.S.C. 321, 331, 352, 355, 361, 362, 371, 374.

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Subpart A—General

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§740.1 Establishment of warning statements.

(a) The label of a cosmetic product shall bear a warning statement whenever necessary or appropriate to prevent a health hazard that may be associated with the product.

(b) The Commissioner of Food and Drugs, either on his own initiative or on behalf of any interested person who has submitted a petition, may publish a proposal to establish or amend, under subpart B of this part, a regulation prescribing a warning for a cosmetic. Any such petition shall include an adequate factual basis to support the petition, shall be in the form set forth in part 10 of this chapter, and will be published for comment if it contains reasonable grounds for the proposed regulation.

[40 FR 8917, Mar. 3, 1975, as amended at 42 FR 15676, Mar. 22, 1977]

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§740.2 Conspicuousness of warning statements.

(a) A warning statement shall appear on the label prominently and conspicuously as compared to other words, statements, designs, or devices and in bold type on contrasting background to render it likely to be read and understood by the ordinary individual under customary conditions of purchase and use, but in no case may the letters and/or numbers be less than $1/16$ inch in height, unless an exemption pursuant to paragraph (b) of this section is established.

(b) If the label of any cosmetic package is too small to accommodate the information as required by this section, the Commissioner may establish by regulation an acceptable alternative method, e.g., type size smaller than $1/16$ inch in height. A petition requesting such a regulation, as an amendment to this section, shall be submitted to the Division of Dockets Management in the form established in part 10 of this chapter.

[40 FR 8917, Mar. 3, 1975, as amended at 42 FR 15676, Mar. 22, 1977; 69 FR 13717, Mar. 24, 2004]

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Subpart B—Warning Statements

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§740.10 Labeling of cosmetic products for which adequate substantiation of safety has not been obtained.

(a) Each ingredient used in a cosmetic product and each finished cosmetic product shall be adequately substantiated for safety prior to marketing. Any such ingredient or product whose safety is not adequately substantiated prior to marketing is misbranded unless it contains the following conspicuous statement on the principal display panel:

Warning—The safety of this product has not been determined.

(b) An ingredient or product having a history of use in or as a cosmetic may at any time have its safety brought into question by new information that in itself is not conclusive. The warning required by paragraph (a) of this section is not required for such an ingredient or product if:

(1) The safety of the ingredient or product had been adequately substantiated prior to development of the new information;

(2) The new information does not demonstrate a hazard to human health; and

(3) Adequate studies are being conducted to determine expeditiously the safety of the ingredient or product.

(c) Paragraph (b) of this section does not constitute an exemption to the adulteration provisions of the Act or to any other requirement in the Act or this chapter.

[40 FR 8917, Mar. 3, 1975]

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§740.11 Cosmetics in self-pressurized containers.

(a)(1) The label of a cosmetic packaged in a self-pressurized container and intended to be expelled from the package under pressure shall bear the following warning:

Warning—Avoid spraying in eyes. Contents under pressure. Do not puncture or incinerate. Do not store at temperature above 120 °F. Keep out of reach of children.

(2) In the case of products intended for use by children, the phrase “except under adult supervision” may be added at the end of the last sentence in the warning required by paragraph (a)(1) of this section.

(3) In the case of products packaged in glass containers, the word “break” may be substituted for the word “puncture” in the warning required by paragraph (a)(1) of this section.

(4) The words “Avoid spraying in eyes” may be deleted from the warning required by paragraph (a)(1) of this section in the case of a product not expelled as a spray.

(b)(1) In addition to the warning required by paragraph (a)(1) of this section, the label of a cosmetic packaged in a self-pressurized container in which the propellant consists in whole or in part of a halocarbon or a hydrocarbon shall bear the following warning:

Warning—Use only as directed. Intentional misuse by deliberately concentrating and inhaling the contents can be harmful or fatal.

(2) The warning required by paragraph (b)(1) of this section is not required for the following products:

(i) Products expelled in the form of a foam or cream, which contain less than 10 percent propellant in the container.

(ii) Products in a container with a physical barrier that prevents escape of the propellant at the time of use.

(iii) Products of a net quantity of contents of less than 2 ozs. that are designed to release a measured amount of product with each valve actuation.

(iv) Products of a net quantity of contents of less than ½ oz.

(c) Labeling requirements for cosmetics packaged in a self- pressurized container containing or manufactured with a chlorofluorocarbon propellant or other ozone-depleting substance designated by the Environmental Protection Agency (EPA) are set forth in 40 CFR part 82.

[40 FR 8917, Mar. 3, 1975, as amended at 42 FR 22033, Apr. 29, 1977; 54 FR 39640, Sept. 27, 1989; 61 FR 20101, May 3, 1996]

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§740.12 Feminine deodorant sprays.

(a) For the purpose of this section, the term “feminine deodorant spray” means any spray deodorant product whose labeling represents or suggests that the product is for use in the female genital area or for use all over the body.

(b) The label of a feminine deodorant spray shall bear the following statement:

Caution—For external use only. Spray at least 8 inches from skin. Do not apply to broken, irritated, or itching skin. Persistent, unusual odor or discharge may indicate conditions for which a physician should be consulted. Discontinue use immediately if rash, irritation, or discomfort develops.

The sentence “Spray at least 8 inches from skin” need not be included in the cautionary statement for products whose expelled contents do not contain a liquified gas propellant such as a halocarbon or hydrocarbon propellant.

(c) Use of the word “hygiene” or “hygienic” or a similar word or words renders any such product misbranded under section 602(a) of the Federal Food, Drug, and Cosmetic Act. The use of any word or words which represent or suggest that such products have a medical usefulness renders such products misbranded under section 502(a) of the Act and illegal new drugs marketed in violation of section 505 of the Act.

[40 FR 8929, Mar. 3, 1975]

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§740.17 Foaming detergent bath products.

(a) For the purpose of this section, a foaming detergent bath product is any product intended to be added to a bath for the purpose of producing foam that contains a surface-active agent serving as a detergent or foaming ingredient.

(b) The label of foaming detergent bath products within the meaning of paragraph (a) of this section, except for those products that are labeled as intended for use exclusively by adults, shall bear adequate directions for safe use and the following caution:

Caution—Use only as directed. Excessive use or prolonged exposure may cause irritation to skin and urinary tract. Discontinue use if rash, redness, or itching occurs. Consult your physician if irritation persists. Keep out of reach of children.

(c) In the case of products intended for use by children, the phrase “except under adult supervision” may be added at the end of the last sentence in the caution required by paragraph (b) of this section.

[51 FR 20475, June 5, 1986]

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§740.18 Coal tar hair dyes posing a risk of cancer.

(a) The principal display panel of the label and any labeling accompanying a coal tar hair dye containing any ingredient listed in paragraph (b) of this section shall bear, in accordance with the requirements of §740.2, the following:

Warning—Contains an ingredient that can penetrate your skin and has been determined to cause cancer in laboratory animals.

(b) Hair dyes containing any of the following ingredients shall comply with the requirements of this section: (1) 4-methoxy-*m*-phenylenediamine (2,4-diaminoanisole) and (2) 4-methoxy-*m*-phenylenediamine sulfate (2,4-diaminoanisole sulfate).

[44 FR 59522, Oct. 16, 1979]

EFFECTIVE DATE NOTE: At 47 FR 7829, Feb. 23, 1982, §740.18 was stayed until further notice, effective Sept. 18, 1980.

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§740.19 Suntanning preparations.

The labeling of suntanning preparations that do not contain a sunscreen ingredient must display the following warning: “Warning—This product does not contain a sunscreen and does not protect against sunburn. Repeated exposure of unprotected skin while tanning may increase the risk of skin aging, skin cancer, and other harmful effects to the skin even if you do not burn.” For purposes of this section, the term “suntanning preparations” includes gels, creams, liquids, and other topical products that are intended to provide cosmetic effects on the skin while tanning through exposure to UV radiation (e.g., moisturizing or conditioning products), or to give the appearance of a tan by imparting color to the skin through the application of approved color additives (e.g., dihydroxyacetone) without the need for exposure to UV radiation. The term “suntanning

preparations" does not include products intended to provide sun protection or otherwise intended to affect the structure or any function of the body.

[64 FR 27693, May 21, 1999]

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Need assistance?

Speaker Biographies

Combiz Richard Abdolrahimi, Esq., J.D., LL.M.
Global Emerging Technology & Innovation Strategist
Senior Advisor Manager
Government & Public Services
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Combiz Richard Abdolrahimi is a U.S. national security lawyer, a global emerging technology and innovation strategist at Deloitte, a former regulator and policymaker, and until recently, he served as a senior policy advisor at the U.S. Department of the Treasury. Combiz has 11 years of public and private sector experience and has worked with senior executives and world leaders from various industries on shaping the business, policy, legal, regulatory, and technology dimensions of Blockchain and distributed ledger technologies (DLT), artificial intelligence and machine learning, digital asset technologies and innovations including cryptocurrency and digital fiat currency, cybersecurity, RegTech, banking and financial services, payments, identity, privacy, risk management and compliance. He co-authored the first U.S. government primer on how Blockchain can enable innovation in government; the first U.S. government primer on how FinTech and emerging technologies can deliver more seamless, safe, efficient, and impactful experiences; and he has held leadership roles on professional boards and government working groups. He serves as Special Advisor & ExecSec to the Chairman of the Federal Identity Forum & Expo (FedID) – which is largest conference and expo run by the U.S. Federal Government focused on public-private outreach and collaboration-building with the worldwide identity community.

Combiz has served extensively in government since he was 19 years old; and has worked on national security, cybersecurity, technology and innovation initiatives, public policy and diplomacy, economic, legislative, regulatory and legal matters. He has also served in the U.S. Senate, The White House, and State Department, where he liaised with government officials and world leaders from over 90 countries and received commendations from Republican and Democratic leadership. Combiz is a recipient of the 2018 Rising Stars Award which recognizes the top 20 U.S. government IT's innovators and emerging leaders; a Fellow with the ALPS Leadership Program; a Fellow with Blockchain in Healthcare Global-IEEE; an editorial board member with Blockchain in Healthcare Today; and Deputy Chair of the American Council for Technology (ACT) and Industry Advisory Council (IAC) Blockchain Forum.

Born in Texas, the son of immigrants, Mr. Abdolrahimi's first job was working the cash register for his family's small business—at the age of 12. He is a graduate of UCLA; American University of Beirut; and Georgetown Law, receiving his B.A., J.D. and LL.M. in national security. Mr. Abdolrahimi speaks several languages critical to U.S. interests and aspires to follow in the footsteps of an American hero, Ambassador Col. Charles W. Hostler, USAF (ret.), and serve as a U.S. Ambassador.

Sheila Arquette is the Executive Director of the National Association of Specialty Pharmacy. She holds a Bachelor of Science degree in Pharmacy from the State University of New York at Buffalo School of Pharmacy. She has extensive practical and leadership experience in retail pharmacy, hospital pharmacy, long-term care consulting and dispensing, in addition to managed care, PBM operations and specialty pharmacy. She is a regular speaker and participant at national pharmacy conferences, roundtables and industry meetings. Sheila has recently been appointed to the University of Pittsburg's Master of Science in Pharmacy Business Administration (MSPBA) Executive Steering Board and serves as a clinical pharmacist consultant to HealthNow New York Inc. She is the host of the NASP Podcast on the Pharmacy Podcast Network.

Sheila was elected to the NASP Board of Directors and received the NASP Distinguished Service Award in September 2016. She also is a long- standing member of AMCP.

Prior joining NASP in February 2017, Sheila was the Director of Pharmacy Services at Independent Health.

Larissa C. Bergin
Partner
Jones Day

Larissa Bergin's practice addresses the antitrust concerns arising from M&A matters, joint ventures, federal investigations, and commercial practices. She has overseen the antitrust aspects of corporate M&A, including due diligence, risk-shift negotiations, Hart-Scott-Rodino (HSR) filings, Second Requests, investigational hearings, integration planning, and consent decrees with federal agencies. She works with clients in a variety of industries, including the technology, health care, retail, and pharmaceutical sectors. Many of Larissa's clients have international reach, and she has been involved in matters that require advocacy before governments throughout Asia, the EU, and North America.

Larissa also advises clients on corporate contracting and operational practices that can run afoul of the antitrust laws, including supplier agreements, information sharing, competitive benchmarking, and Robinson-Patman Act pricing matters.

At the start of her career, Larissa clerked at the U.S. Court of Federal Claims, where she addressed intellectual property, tax, and government contract issues, including Serco, Inc. v. United States (also referred to as the Alliant protest), a bid-protest case involving a $50 billion procurement for government-wide information technology and services.

Larissa is a member of the Antitrust Section of the American Bar Association and is secretary of the New York State Bar Association, Food, Drug, and Cosmetics Law Section. She is admitted in the New York, Connecticut, and District of Columbia bars.

Larissa has been quoted on MSNBC regarding how Obamacare has affected M&A activity and in Getting the Deal Through on generic drug approval.

Sharon Blinkoff

Sharon Blinkoff represents manufacturers, marketers, and distributors of cosmetics, dietary supplements, over the counter drugs, and medical devices as well as beauty appliances and other consumer products and luxury goods. She regularly advises clients on compliance with the laws enforced by the FDA, CPSC, and the FTC, and obtaining FDA registrations and 510k premarket clearances.

For many years Sharon has played a leadership role in the Cosmetics and Personal Care Industry serving on the Board of Directors and as Corporate Secretary for the Independent Cosmetic Manufacturers and Distributors (ICMAD) Trade Association. Sharon, on behalf of ICMAD, has served as part of the industry negotiating team that met with representatives of the US FDA to develop a framework for new Cosmetic legislation. She has also been an active participant on behalf of the industry, by submitting comments on FDA's proposed changes to the OTC Monograph proceedings and the proposal to require IND's for cosmetic testing, as well as other regulatory proceedings both state and federal that impact on the Cosmetic and Personal Care industry.

Having served as Division and Regulatory Counsel for Bristol-Myers Squibb/Fortis Clairol Division, as well as Senior Counsel for Revlon, Sharon brings considerable experience in representing regulated businesses on a broad range of regulatory and business matters. She also served as General Counsel to Ethan Allen Inc. and was part of the management group that restructured the company and took it public. With her broad regulatory experience and business background, She brings considerable knowledge and expertise to the challenges faced by her clients. Having spent her early career as a patent attorney for the National Institutes of Health, Sharon also brings a keen understanding of the technical side of the regulatory process and the interplay between regulatory issues and IP assets and how they relate to the client's business strategy.

Sharon has successfully defended clients in regulatory proceedings before the FDA and the FTC, and has instituted and defended clients in advertising challenges before the NAD, ERSP and the FTC as well as in Lanham Act litigations. She has also assisted in the structuring business transactions involving regulated products and industries, including corporate acquisitions and divestitures, public offerings, joint venture and distribution agreements.

Professional Affiliations and Recognitions

- Member, Bar Association of the City of New York
- Member, New York State Bar Association FDA section

- Member, American Bar Association Consumer Protection Section
- Member, the Society of Cosmetic Chemists
- Member, Board of Directors and Corporate Secretary of the Independent Cosmetic Manufacturers and Distributors Association

THOMAS COHN is Director and Senior Counsel, Sales & Marketing at New Avon LLC in New York City. Mr. Cohn graduated from Yale College and Boston University School of Law, and he was admitted to the New York State Bar in 1999.

Mr. Cohn has overall responsibility for providing legal advice regarding Avon's marketing, advertising and social media; promotions, sweepstakes and contests; sales, merchandising and pricing. In addition, he works closely with marketing colleagues and is responsible for claim substantiation and challenges, product labeling review, promotions/sweepstakes/contests, contract drafting and advertising review, including TV, print, brochure, and online/digital marketing. He also advises on product innovation, pricing and other merchandising matters, as well as ensuring compliance with regulatory requirements, including the FTC, FDA and other federal and state regulatory agencies.

Mr. Cohn also provides legal support in the area of intellectual property, including managing trademarks, such as clearance, prosecution, registration, portfolio management, as well as licensing for the product lines and advising on day-to-day trademark matters, domain names, copyrights, rights of publicity, and patents, as needed. He also works with the sales and commercial teams, including advising on regulatory issues, such as FTC/state law compliance regarding multi-level marketing, earnings opportunity, and incentive programs.

Mr. Cohn coordinates Avon's governmental affairs, working with national trade associations such as ICMAD, DSA and CRN, and serves on the task force creating DSA's new self-regulatory program with the Council of Better Business Bureaus. He is a former Northeast Regional Director of the Federal Trade Commission. Mr. Cohn is also a regular speaker and commentator at consumer law seminars and conferences.

Colleen Heisey
Partner
Jones Day

Colleen Heisey's practice focuses on food and drug law with a particular emphasis on product promotion and advertising, compliance counseling, good manufacturing practice requirements, product recalls, FDA inspection, competitor issues, and enforcement actions. She has advised on issues surrounding the regulation of drug, biological, food, dietary supplement, medical device, and cosmetic products by the FDA, USDA, and other federal and state agencies.

Colleen has substantial experience with regulatory oversight and compliance assessment for due diligence audits of drug, medical device, and food companies, including those related to product safety, product labeling, product marketing and advertising, and consumer complaints. She regularly provides legal support for pharmaceutical and device advertising and promotional activities, sales and marketing, and development of practitioner-oriented and direct-to-consumer print and broadcast advertising. Colleen has conducted audits and inspections of pharmaceutical and medical device company policies, procedures, and programs, including drug sampling, adverse event reporting, medical information management, and unsolicited requests. She has advised clients regarding matters related to the False Claims Act and Anti-Kickback Statute, reviewed and commented on strength of clinical trial designs in drug and device development and as potential support of product marketing, and has assessed proposed brand names for drug products in development for potential claims and product confusion, including appraisal of drug name similarity reports by third-party vendors. She has worked with regulated industry to develop and implement comprehensive regulatory compliance programs.

Colleen has written extensively on the food and drug industry.

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EDUCATION

- State University of New York - Buffalo (MPH)
- State University of New York - Buffalo (JD, cum laude)
- State University of New York - Geneseo (BA, summa cum laude)

ADMISSIONS

- New York

Bethany is nationally recognized for her experience and insight on FDA matters and advises businesses on both pre- and post-market issues, including everything from FDA submissions and communications strategies to post-approval compliance. Bethany also helps international and US companies enter and navigate the US health care market. She's adept at helping clients identify technologies that are likely to complement the health care delivery system, clear FDA regulatory hurdles, *and* provide a healthy return on investment. She also has an exceptional understanding of health care reimbursement issues.

Bethany is Chair of the firm's FDA practice and leverages deep FDA regulatory experience and exceptional knowledge of the health care delivery system to help international and domestic health technology companies enter and navigate the US health care market. Bethany helps companies manage the full range of FDA regulation issues, from inspections and investigations through complex regulatory challenges affecting everything from product approvals and product labeling to collaborative research, supply, and distribution agreements. She focuses on mission critical strategic engagements, including all aspects of FDA communications. Her client engagements regularly span the full scope of pre-market and post-market issues, from devising unique regulatory strategies that are then implemented through FDA submissions and complex interactions with the FDA, including post-approval compliance and enforcement. Bethany's representative clients include medical device, drug, combination product, diagnostic, biologic and regenerative medicine, cosmetic, dietary supplement and food industry companies.

Through her extensive representation of health care provider businesses, she has developed an understanding of compliance issues and of the US health care reimbursement system that far surpasses that of most FDA lawyers. She uses her strengths in these areas to provide clients with insight on regulatory policy, reimbursement issues, and pricing to shape innovation, and helps them use that knowledge to develop viable value propositions within the constraints of the evolving health care delivery system. She advises clients on laws applying to referral relationships, clinical trial compliance, licensure, and security and privacy issues as well as on the ins and outs of government and third-party reimbursement. Clients rely on Bethany's practical guidance to help them invest and collaborate strategically, by identifying technologies that are likely to complement the health care delivery system, clear FDA regulatory hurdles, *and* provide a healthy return on investment.

Before joining Mintz, Bethany served as the co-leader of the FDA and medical technology services team in the New York office of another law firm. She works with academic centers to educate future business leaders on relevant health care regulatory issues, and is frequently invited to speak on issues concerning FDA regulations, health care reimbursement, and pricing.

Recognition & Awards

- Lexology and the ILO: Client Choice Award
- Included on the New York Super Lawyers Rising Star: Food & Drugs, Health Care, and Technology Transactions lists (2015 - 2018)
- Chambers USA: "Up-and-Coming" lawyer, New York Healthcare category (2012 ? 2014)
- American Bar Association and Bureau of National Affairs: Excellence in Health Law (2005)
- Recognized by The Legal 500 United States for Healthcare: Service Providers (2017)
- Environment and Society Institute, Lester Milbrath fellowship

Involvements

- Member, executive committee, Food, Drug, and Cosmetic Law Section, New York State Bar Association

- Member, Editorial Advisory Board, BNA Medical Devices Law & Industry Report
- Member, Regulatory Affairs Professional Society
- Member, American Health Lawyers Association
- Appointed Member, New York State Bar's Committee on Cannabis Law
- Executive committee, Kevin Guest House for Patient Families, Buffalo, NY (until 2012)
- Board of directors, MedTech (2014 ? 2015)
- Board of directors, NY Data Protection Review Board (2010 ? 2013)

Experience

- Provided strategic counsel to a start-up medical application company that has devised a method to detect mild cognitive impairment as a precursor to more significant cognitive diseases.
- Represent a national IVF clinic and management provider in drug delivery, pharmacy relationships, and delivery of care issues.
- Counseled a cosmetic company on its response to an FDA Warning Letter related to the use of drug claims to promote cosmetic products and assisted in the company's implementation of internal processes and procedures to avoid similar issues in the future.
- Assisted multiple pharmacy clients in determining whether to register with FDA as an Outsourcing Facility and advised them regarding the establishment of such operations.
- Advise innovative drug development client on regulatory strategy following Phase II clinical study data analysis.
- Advise a food manufacturing company on multiple product line contract manufacturing arrangements and negotiated supply and quality agreements.
- Analyzed the impact of proposed Medicare National Coverage Decision on an integrated FDA and reimbursement strategy for a next generation sequencing cancer test and drafted comments to CMS.
- Guided a medical device manufacturer through multiple FDA inspections and developed effective and sustainable corrective actions to address deficiencies and avoid focused FDA enforcement.
- Participated in marketing and labeling pre-launch team, working side by side with biological client team to craft marketing messages and product labeling for product launch.
- Provided legal and regulatory advice to consumer app software collecting symptoms and providing guidance on possible next steps, including commercial agreements and new feature development.
- Conducted a regulatory assessment and classification of software product used to support monitoring and management of patients with chronic obstructive pulmonary disorder.
- Advised on legal and regulatory issues surrounding market launch of a software solution to gather patient data from peripheral devices and coordinate a communication and management platform with their physician, including licensing arrangements, clinical study agreements, and quality and supply agreements.

Practices

- **Consumer Product Safety**
- **FDA Regulatory**
- **Clinical Trials & Research**
- **Health Care Compliance, Fraud & Abuse, and Regulatory Counseling**
- **Medicare, Medicaid & Commerical Coverage & Reimbursement**
- **Health Care Enforcement & Investigations**
- **Health Care Transactional Due Diligence**
- **Israel**

Industries

- **Health Care**
- **Life Sciences**
- **PBMs & Pharmacies**
- **Digital Health**
- **Laboratories**
- **Diagnostics**
- **Hospitals & Health Systems**
- **MedTech, Tools & Devices**
- **Biosimilars**
- **Artificial Intelligence**

News & Press

FDA Focus: What Mintz's Practice Chair Is Watching
October 2, 2018 | **Law360**

Device Experts: Expanded Special 510(k) Good For Software, Review Times
October 2, 2018 | **Inside Health Policy**

Twenty-Four Mintz Attorneys Named 2018 New York Super Lawyers and Rising Stars
September 19, 2018

Device Lawyer: Guidance Shows FDA OK With More Premarket Risk
September 6, 2018 | **Inside Health Policy**

Industry Attorneys: New Pre-Cert Model Vague On Requirement Details
June 21, 2018 | **Inside Health Policy**

Artificial intelligence is evolving fast. Can the FDA keep up?
May 25, 2018 | **STAT News**

Medical device recalls reach historic levels in 2018 with software as leading cause
May 9, 2018 | **FierceHealthcare**

Expanded 510(k) Option Doesn't Quell Industry Skepticism Over Pathway
April 20, 2018 | **Inside Health Policy**

FDA medical device proposal may skirt the law: legal experts
December 19, 2017 | **Reuters**

FDA proposal on health software provides no clarity on artificial intelligence
December 8, 2017 | **STAT News**

After a 6-year wait, FDA’s clinical decision support guidelines get a mixed reaction
December 7, 2017 | **FierceHealthcare**

Twenty-Seven Mintz Attorneys Named 2017 New York Super Lawyers and Rising Stars
September 20, 2017

Mintz Attorneys and Practice Areas Recognized By 2017 Legal 500 Guide
August 17, 2017

9 companies will play a huge role in shaping the FDA’s novel approach to digital health
August 2, 2017 | **FierceHealthcare**

FDA unveils precertification pilot program for digital health technology, maps out upcoming guidance
July 28, 2017 | **FierceHealthcare**

“Will a New FDA User Fee Discourage Medical Device Innovation?”
June 12, 2017

Trump’s Budget Would Add $313M to Medical Device User Fees, but Congress is Unlikely to Follow Through
May 25, 2017

3 Ways Trump’s FDA Nominee Could Reshape Digital Health
March 16, 2017

New FDA Enforcement Stats Show Shifting Targets
February 13, 2017

High Expectations During the Trump Administration
January 23, 2017 | **New York Law Journal**

21st Century Cures Act & Real World Evidence: Device Policy as Foundation
January 23, 2017

The FDA targeted DTC, video, unapproved drug promotion in 2016
January 18, 2017

Health Care Enforcement Review And 2017 Outlook: Part 1
January 13, 2017

Attorney: Combo Review Issues Signal Hurdles For FDA Intercenter Institutes
December 16, 2016 | **Inside Health Policy**

Cures Exempts Some Medical Software; More Clarity Needed, Attorneys Say
December 15, 2016 | **Inside Health Policy**

Senate passes landmark 21st Century Cures, sending legislation to Obama
December 7, 2016 | **STAT News**

Twenty-Eight Mintz Attorneys Named 2016 New York Super Lawyers and Rising Stars
September 21, 2016

Questions Of Culpability After 8th Circ. Egg Exec Decision
August 1, 2016

Akin Gump Health Leader Heads In-House, Plus More Lateral Moves
March 22, 2016

Movers & Shakers: Pamplona Recruits Pacala For Healthcare Investments
March 15, 2016

Mintz Bolsters Health Law Practice in New York with Addition of Bethany Hills and Benjamin Zegarelli
March 07, 2016

Events

//
Nov 1 2018
2018 Technology in Psychiatry Summit: Closing Gaps in Translation
De-Risking Digital Development: Innovations in Substance Use Disorder Treatment

Boston, MA

// SPEAKER
Oct 10 2018
Retail Industry Leaders Association (RILA) Retail Law Conference
Austin, Texas

// SPEAKER
Jul 18 2018
Rare Disease Symposium
Westchester Biotech Project

New York, NY

// MODERATOR
Jun 1 2018
6th Annual World Life Sciences Conference
International Bar Association

InterContinental Boston 510 Atlantic Avenue Boston, MA 02210

// MODERATOR
Mar 29 2018
Risks and Rewards of Accelerated FDA Pathways
Mintz Levin

Boston, MA

// PANELIST
Mar 11 2018
BPIP 6th Annual Conference
Best Practices in Intellectual Property

Sheraton Tel Aviv Tel Aviv, Israel

// SPEAKER
Feb 15 2018
Part III: The Impact of Cures on the FDA
Webinar

// MODERATOR
Feb 7 2018
Conducting Multi-Jurisdictional Trials: Understanding Changes in the US and EU Part II
Webinar

// SPEAKER
Jan 24 2018
Part I - Multi-Jurisdictional Clinical Trials: Understanding Changes in the US and EU
Webinar

// MODERATOR
Nov 21 2017
IP Course: Medical Device Regulatory Lecture
New York, NY

// PANELIST
Nov 16 2017
Digital Health - Regulatory Process Panel
New York, NY

// MODERATOR
Nov 14 2017
IP Course: Therapeutics-focused Regulatory Lecture
New York, NY

// PANELIST
May 24 2017
ATA 2017

// PANELIST
May 11 2017
The NewYorkBIO 2017 Annual Conference
New York, NY

// FACULTY
Feb 10 2017
Trump's First 100 Days, Part IV: AMCs, Life Sciences, Pharma, and Medical Device Companies
AHLA

Webinar

// SPEAKER
Jan 26 2017
Food, Drug & Cosmetic Law Section Meeting
New York State Bar Association

New York, NY

// SPEAKER
Jan 24 2017
FDA in 2017: What to Expect?
New York, NY

// PANELIST
Jan 18 2017
Impact of the Cures Act on the Medical Device Industry
MassMEDIC

Webinar

// SPEAKER
Jan 12 2017

Part I: Introduction to the 21st Century Cures Act
Webinar

// SPEAKER
Nov 8 2016
Icahn School of Medicine at Mount Sinai Program
ISMMS

// SPEAKER
Oct 21 2016
Critical Path Life Sciences Accelerator Program
University at Buffalo Technology Incubator

// SPEAKER
Sep 29 2016
Medical Device Reimbursement 201 Workshop
AdvaMed

Washington, DC

// PANELIST
Sep 22 2016
Mobile Medical Applications: Navigating Regulatory, Profitability, and Patentability
Boston, MA

// PANELIST
Sep 19 2016
2016 RAPS Annual Meeting

Aaron L. Josephson

Senior Director
ALJosephson@mlstrategies.com
+1.202.434.7454

Aaron is based in our Washington, DC office and is a Senior Director of ML Strategies. He advises clients on health care policy issues related to medical devices and pharmaceuticals.

Prior to joining ML Strategies, Aaron spent 10 years with the US Food and Drug Administration, most recently as a senior policy advisor in the Center for Devices and Radiological Health where he led legislative policy development activities related to all aspects of medical device regulation and oversight. He also apprised members of Congress and their staffs about FDA policies and programs and advised multiple FDA Commissioners and other senior officials on strategy and content for meetings with Congress, industry representatives, and other stakeholders. In addition to negotiating the reauthorization of the medical device user fee program (MDUFA), Aaron led FDA's implementation of key provisions of the 21st Century Cures Act and the FDA Reauthorization Act.

Earlier, Aaron was a budget analyst in the FDA's Center for Drug Evaluation and Research, where he developed the center's annual budget and provided information to the Congressional Budget Office (CBO) and congressional authorizers. He began his FDA career in the Center for Biologics Evaluation and Research as an information management specialist responsible for data analyses to support FDA policies and programs.

During his tenure with the FDA, Aaron won numerous agency awards, including the Lireka P. Joseph Award for Excellence in Public Health Communication or Education. He also received special recognition from multiple FDA Commissioners, including a June 2017 special citation for outstanding and sustained performance in the negotiation and reauthorization of MDUFA IV and an August 2016 award for contributions to the 21st Century Cures Act.

Aaron earned a master's certificate in project management from the George Washington University School of Business and is certified by the American Society for Quality as a quality improvement associate.

EDUCATION

- Johns Hopkins University (MS)
- University of Virginia (BA)

Ron Lanton III, Esq., has over 25 years of experience in government affairs at the municipal, state, and federal government levels, with 15 years dedicated to the healthcare sector. He is currently the executive director and head lobbyist at Frier Levitt Government Affairs, LLC and senior counsel at Frier Levitt. He frequently consults Wall Street firms on financial issues related to the healthcare sector.

Lanton is a featured industry speaker on issues such as pharmaceutical safety and healthcare cost containment, and he has authored numerous articles regarding pharmacy and healthcare law. He earned a B.A. from Miami University and a J.D. from The Ohio State University. He is also the chair of the Biologics Committee for the New York Bar Association.

Janet B. Linn

Janet B. Linn is intellectual property litigator at Tarter Krinsky & Drogin, with more than 25 years' experience ligating patent, trademark, unfair competition, trade secret and copyright cases, as well as advising on patent prosecution, and providing patent validity and infringement opinions, in a broad range of technologies including pharmaceuticals, medical devices, consumer products and mechanical devices. She has extensive experience in pharmaceutical patent litigation, representing both branded and generic companies, and has acted as trial counsel in patent (Hatch-Waxman), trade secret and antitrust litigation involving pharmaceuticals with annual billion dollar sales.

Active in the profession, Ms. Linn is a member and former Chair of the Patents Committee of Association of the Bar of the City of New York, the current Vice Chair of the Food Drug & Cosmetic Section of the New York State Bar Association, a member of Women in Licensing, and a frequent author and lecturer on intellectual property issues

Brian Malkin

Brian is an attorney in Arent Fox's FDA, Intellectual Property, and Health Care Groups. Brian has more than 24 years of food and drug law practice and over 13 years of intellectual property law practice. In particular, his practice includes the interrelation between patent law and food and drug law. Brian's regulatory experience includes all types of FDA-regulated products: drugs (including animal drugs), biologics, medical devices, foods and dietary supplements, tobacco products, and cosmetics. Brian's intellectual property experience includes FDA and patent litigation for both innovator and generic companies. Brian began his legal career as a regulatory counsel at the U.S. Food and Drug Administration, where he worked for more than nine years in both the Office of the Commissioner and the Center for Drug Evaluation and Research. At FDA he focused on new product evaluations, compliance issues related to clinical investigations and intellectual property (e.g., patent term restoration), and Brian also was an agency liaison for the Institute of Medicine. Brian's work resulted in new product approvals as well as new industry guidance documents and policies, such as the animal efficacy rule for counter-terrorism products. Following several years of practice in an FDA law firm, Brian recognized an unmet need to understand both food and drug and intellectual property law for life cycle management and diligence, particularly concerning products affected by the Hatch-Waxman Act such as generic and 505(b)(2) new drug applications. As a result, Brian returned to university to obtain a Bachelor of Science degree in biochemistry. Prior to joining Arent Fox, Brian practiced for more than nine years at an intellectual property law firm, where he worked on a variety of new product evaluations, FDA and patent litigations, due diligence projects, patent prosecutions, and licensing and commercial transactions and has also led an FDA Group at an international law firm for nearly three years.

Lesley R. Maloney

Lesley R. Maloney, Pharm.D., is Head, U.S. Regulatory Policy for Roche Diagnostics. In that role, she is responsible for guiding Roche Diagnostics' regulatory policy efforts in the United States. In addition, she is also responsible for specific regulatory policy efforts related to digital health, including Roche's involvement in the FDA Software Precertification Pilot Program. Dr. Maloney joined Roche Diagnostics in 2017. Prior to joining Roche Diagnostics, she worked for the U.S. Food and Drug Administration in the Office of the Commissioner, where she served in various roles, including Deputy Chief of Staff, Senior Policy Advisor, and Deputy Associate Commissioner for External Affairs. While at the FDA, Dr. Maloney worked on such medical product policy issues as the 21st Century Cures Act legislation, improvements related to combination product oversight, and development of a new regulatory framework for over-the-counter medications. Dr. Maloney also has experience in the pharmaceutical industry, a quality improvement organization, and a national pharmacist association. Dr. Maloney holds a doctor of pharmacy degree from the University of Oklahoma and did an Executive Residency in Association Leadership and Management at the American Society of Health-Systems Pharmacists.

Victoria J. Maniatis graduated with a BA from the Pennsylvania State University in 1990, a J.D. from Hofstra University School of Law in 1993 and has been admitted to practice law in New York and New Jersey since 1994. During law School, Ms. Maniatis interned for two summers with the Middlesex County Prosecutor's office. Once admitted, she started practicing as a general negligence defense attorney, before transitioning into the field of Plaintiffs' Mass Tort in 1998 at Kreindler & Kreindler litigating Aviation disasters. Currently she is a partner at Sanders Phillips Grossman where she works on mass tort cases involving pharmaceuticals and medical devices, the field she has worked in for seventeen years. She is a frequent invited lecturer and moderator on a wide variety of pharmaceutical and mass tort cases including, Opioids, Trans Vaginal Mesh, Fosamax, Ortho Evra, Risperdal, Propecia, Avandia, Onglyza, as well as several medical devices. She has also published articles on pharmaceuticals and vaccines. She currently serves on her firm's Opioids Task Force educating lawyers and municipalities about the epidemic. Ms. Maniatis has been appointed by State and Federal Judges to serve as lead counsel and on Plaintiffs' steering committees. She currently acts as lead counsel in the New Jersey Propecia Multi County Litigation. She also serves on the Fosamax Femur PSC (DNJ), the Transvaginal Mesh MDL PSC's in the Bard, Boston Scientific, American Medical Systems and Ethicon cases (DWV), the Benicar MDL PSC (DNJ) as well as the Talcum Powder MDL PSC (DNJ). Vicki has also regularly performs common benefit work outside her PSC appointments.

Vicki performs all levels of bellwether trial case specific work up including, plaintiff, spouse and family member depositions, implanting, explanting, treating physicians, sales representative and expert depositions, for over 30 cases in several mass torts including TVM, Mirena and Propecia cases.

Vicki has taken part in researching, meeting, retaining, working with experts for depositions and all levels of preparation in several litigations she has worked on and can provide additional information in this regard (subject to strategy and attorney work product).

Vicki has participated in focus group/mock trial scenarios for medical malpractice, aviation disasters, and pharmaceutical cases. She has presented as counsel and witnesses for Plaintiff and defense in Mock trials, and focus groups.

Vicki has been recognized as a Top Attorney of the NY Metro Area and Top Woman Attorney in the NY Metro Area (2013 to date). She is an active participant in the American Association for Justice (AAJ), New Jersey Association for Justice and New York State Trial Lawyers Association (NYSTLA). Ms. Maniatis serves as a founding member of Mass Tort Med School, an annual medical seminar for Plaintiffs' attorneys that offers numerous physician speakers and cutting edge medical issues. She previously served as a committee co-chair for the Women En Mass group. Ms. Maniatis in an active runner and triathlete having completed Marathons, half iron and full Ironman races. She also serves as an Advisory Council Member to the Academy for Biotechnology of the Morris County Vocational School District & Mountain Lakes HS.

A Partner with Dalimonte Rueb LLP, Jennifer Orendi currently contributes several years of experience in law and science to serve individuals adversely affected by dangerous products, including pharmaceuticals and medical devices. Her background in neuroscience research, understanding of neurologic injuries, and laboratory experience prior to law school compliment her aptitude for helping to build cases based upon scientific data and analyses. Prior to law school, Ms. Orendi graduated with honors from Carnegie Mellon University, where she was awarded one of the first undergraduate fellowships by the National Institute of Mental Health (NIMH). She continued her research at laboratories at the University of Pittsburgh Medical Center (UPMC) and at the University of Wisconsin, and then attended Illinois Institute of Technology's Chicago-Kent College of Law, where she earned her Juris Doctor degree with a Certificate in Intellectual Property Law.

Ms. Orendi has managed and litigated hundreds of individual pharmaceutical and medical device product liability cases from intake to resolution and has contributed her passion for science and medicine to several Federal Multi District Litigations (MDLs), including Fen-Phen, Phenylpropanolamine Products, Zyprexa, Vioxx, Ortho Evra, and Pradaxa. She enjoys applying her knowledge of medical facts and prognoses toward the negotiation of claims to help the injured move forward. She is especially interested in legal issues regarding OTC and cosmetic products marketed and sold specifically to women and girls, and in injuries based in neurologic, endocrine and psychiatric manifestations.

Ms. Orendi leads Dalimonte Rueb's efforts on behalf of injured women in the Talc, Taxotere, and Mirena litigations, and was appointed to the Plaintiffs' Steering Committee in *In Re: Mirena IUS Levonorgestrel-Related Products Liability Litigation (No. II),* MDL No. 2767 (Southern District of New York). Before joining Dalimonte Rueb LLP, Ms. Orendi worked on behalf of injured individuals at a nationally-acclaimed law firm, and for a large law firm specializing in food and drug regulatory law, both in Washington, DC. Having completed the program at The Aveda Institute in Washington, DC, Ms. Orendi is also a licensed Cosmetologist.

Kelly Ryan

Kelly Ryan is Senior Director, State Advocacy at PhRMA and provides policy support for New York, Maine, Vermont, New Hampshire, Connecticut, and Rhode Island. Prior to joining PhRMA, Kelly served as Senior Associate General Counsel/Director of Regulatory Affairs at United Healthcare, where she provided regulatory counsel for commercial lines of business in the New York market, and was a Principal in Hinman Straub's Health Law and Government Relations practice groups. While at Hinman Straub, Kelly was a key member of PhRMA's New York team for several years and developed an expertise in a range of health and biotech issues through her representation of stakeholders including health insurers, medical schools and research facilities. She also previously served as legislative counsel to NY State Senator Martin Golden. Kelly is a graduate of Russell Sage College and the Ohio State University School of Law. She is a member of the New York State Bar.

Bruce S. Weintraub

Bruce S. Weintraub is Senior Corporate Counsel in the Legal Division at Pfizer Inc in New York, NY. He is a Core Negotiator for the Global IP Transactions Team at Pfizer Inc. This Team supports Worldwide Business Development, Worldwide Research & Development and Strategic Alliances at Pfizer Inc. Prior to this position, Mr. Weintraub managed patent licensing, R&D collaboration agreements, acquisitions and due diligence for the Pfizer Animal Health division. He graduated from Benjamin N. Cardozo School of Law and is admitted to practice in New York. Mr. Weintraub is a regular speaker and commentator at businessjseminars and conferences.

Howard A. Zucker, M.D., J.D.

Dr. Howard A. Zucker is Commissioner of Health for New York State. As the state's chief physician, Dr. Zucker leads initiatives to combat the opioids crisis, strengthen environmental health and end the AIDS epidemic in New York. Since his arrival at the helm of the NYS Department of Health, he has established a network of hospitals equipped to treat Ebola, implemented programs to address the threat of Zika and spearheaded efforts to combat antimicrobial resistance.

Dr. Zucker oversaw the launch of the state's medical marijuana program and continues to update the program to accommodate evolving needs. He also developed numerous campaigns to address major public health issues, including lead contamination, legionella and breast cancer screenings. His extensive review of scientific literature led the state to reject hydrofracking in its borders.

As Commissioner, Dr. Zucker presides over the state's Medicaid program, the New York State Public Health and Health Planning Council, and the Wadsworth Center, New York's premier public health lab. He also oversees the entire health care workforce, as well as health care facilities, including hospitals, long-term care and nursing homes.

In his previous role as first deputy commissioner, Dr. Zucker worked on the state Department of Health's preparedness and response initiatives in natural disasters and emergencies. He collaborated closely with the New York City Department of Health and Mental Hygiene and other health-related entities in the city.

A native of the Bronx, Dr. Zucker earned his M.D. from George Washington University School of Medicine at age 22, becoming one of America's youngest doctors. He is board-certified in six specialties/subspecialties and trained in pediatrics at Johns Hopkins Hospital, anesthesiology at the Hospital of the University of Pennsylvania, pediatric critical care medicine/pediatric anesthesiology at The Children's Hospital of Philadelphia, and pediatric cardiology at Children's Hospital Boston/Harvard Medical School.

Before joining the state Department of Health in September 2013, Dr. Zucker was a professor of clinical anesthesiology at Albert Einstein College of Medicine of Yeshiva University and pediatric cardiac anesthesiologist at Montefiore Medical Center in the Bronx. He was an adjunct professor at Georgetown University Law School, where he taught biosecurity law.

His vast experience in public policy began as a White House Fellow under then-Health and Human Services Secretary Tommy Thompson. Subsequently he became the Deputy Assistant Secretary of Health where he developed the nation's Medical Reserve Corps, which today is run by the U.S. Surgeon General and includes more than 200,000 volunteers across nearly 1000 programs. He also worked on the development of the initial SARS preparedness plan, the anthrax crisis, and the National Institutes of Health autism summit, and led a multidisciplinary team on the issue of tissue engineering/regenerative medicine. Dr. Zucker advanced his public policy experience while serving as an Institute of Politics Resident Fellow at Harvard Kennedy School and later as a Presidential Leadership Scholar.

Dr. Zucker is recognized internationally for his work to advance global health. As senior advisor in the Division of Global Health and Human Rights at Massachusetts General Hospital, he leads a team of experts in developing a community peace index, a research initiative aimed at identifying the effectiveness of peace intervention programs in countries impacted by war, political strife and economic instability.

Previously, he served as Assistant Director-General of the World Health Organization (WHO) in charge of the Health Technology & Pharmaceuticals cluster. In this capacity, Dr. Zucker was the highest ranked American at the WHO and spearheaded efforts to globally combat counterfeit medicines as well as address the interface between intellectual property rights, innovation and public health. He is also a member of the Council on Foreign Relations, Council for Emerging National Security Affairs, and was a "high-level expert" on public health for NATO.

While working on a public-private partnership with an educational technology company, he developed The Afghan Family Health Book, a health literacy project that has educated millions of women in Afghanistan. Dr. Zucker has traveled to China and Haiti on medical missions and spoken extensively throughout the United States on national health policy issues as well as internationally on global health challenges.

Dr. Zucker served as associate professor of clinical pediatrics and anesthesiology at Columbia University College of Physicians & Surgeons and pediatric director of the ICU at New York Presbyterian Hospital, where he launched the restructuring of the critical care complex both from a clinical care delivery standpoint as well as the physical environment. He has held academic appointments at Yale University School of Medicine and the National Institutes of Health, and as a research affiliate in the Center for Space Research at the Massachusetts Institute of Technology.

Dr. Zucker received his B.S. degree from McGill University. As a student at McGill, he helped design zero-gravity medical experiments that ultimately were conducted aboard several Space Shuttle missions. Today, he serves on the Board of Directors of the nongovernmental organization that oversees the U.S. National Lab on the International Space Station.

Dr. Zucker holds a J.D. from Fordham University Law School, a LL.M. from Columbia Law School and a postgraduate diploma from the London School of Hygiene and Tropical Medicine. He holds an honorary Doctor of Science from the Icahn School of Medicine at Mount Sinai and an honorary Doctor of Humane Letters from the Albany College of Pharmacy and Health Sciences. A former ABC World News' Person of the Week and Columbia University Pediatrics Teacher of the Year, Dr. Zucker has been listed in Best Doctors in America as well as Who's Who in the World. He is a member of the medical honor society, Alpha Omega Alpha, and the Bar of the U.S. Supreme Court.