New York State Bar Association

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COMMENTS SUBMITTED ON BEHALF OF THE HEALTH LAW SECTION COMMITTEE ON MEDICAL RESEARCH AND BIOTECHNOLOGY; AND THE FOOD, DRUG AND COSMETIC LAW SECITON

on

U.S. Food and Drug Administration (FDA) Guidance entitled "Framework for Regulatory Oversight of Laboratory Developed Tests (LDTs)

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As members of the New York State Bar Association Health Law Section, Committee on Medical Research and Biotechnology, and Food, Drug and Cosmetic Law Section we are pleased to offer these comments on the U.S. Food and Drug Administration (FDA) Guidance entitled "Framework for Regulatory Oversight of Laboratory Developed Tests (LDTs)" issued on October 3, 2014.

The key elements of these comments include the following, each of which is more fully described below:

1) **Overarching Concern**: The agency should proceed with expanded registration and data collection for ALL LDTs to better understand the current status of the clinical laboratory universe and prior to development of further regulatory guidance.

2) Clinical Laboratory Improvement Act (CLIA) **CLIA Regulatory Oversight:** The FDA may wish to fully explore with its sister agency Centers for Medicare and Medicaid (CMS) the expansion and modernization of the existing system involving CLIA regulatory oversight before creating a parallel but divergent additional regulatory oversight burden.

3) **Technical Aspects**: Develop further clear, specific, detailed guidance on technical aspects of any future intended regulatory oversight or guidance including:

A) **Clinical Validity:** Clarification of the definition of and metrics to be used in calculation of the critical component of "clinical validity."

B) **Bioinformatics**: Use of bioinformatics and software technology in test interpretation and reporting is becoming the norm, not an exception. As a critical component of the test, its use should not exclude the test from laboratory development and innovation or necessarily subject the test to enhanced regulatory burden.

C) **Definition of Healthcare System**: The definition of a health care system or facility requires further consideration. Reference to laboratory testing performed "out of network" should not exclude use or development of laboratory innovation and "new" tests.

D) **Laboratory Test Definition**: Clarification of the definition of "laboratory test" and its components including those not subject to FDA statutory/regulatory authority as the practice of medicine.

E) "**Rare Diseases"** and "**Unmet Need**": Reconsideration of the "rare disease" and "unmet need" category definitions as tests for these situations, while needed without undue regulatory burden, may also represent situations of extreme patient risk.

F) **Analyte Specific Reagents (ASRs)**: The "ASR rule" will require revisiting open communication between manufacturers and laboratories, or the agency might consider revisiting IVD oversight of ASR manufacturers.

G) "**Research Use Only**": RUO, IUO, and other products used by laboratories in test innovation must be considered including possible application of IVD oversight of such manufacturers, rather than continued current regulatory discretion exercised toward such manufacturers while proposing to shift the regulatory burden to the laboratories.

H) **Contract Manufacturing**: Contract manufacturing of test components enhances test component quality and must not exclude test innovation from using such materials.

1) Overarching Concern:

We recognize the need for the regulatory oversight of the quality, safety and efficacy of laboratory developed tests (LDTs). As the FDA has stated the numbers and diversity of laboratory developed tests and the institutional demographics of the laboratories that offer such testing has significantly changed since the agency was tasked with the authority to oversee in vitro diagnostic laboratory tests as medical devices (1976). This expanded and extraordinarily diverse universe would suggest that the FDA consider further extending the phase in period of any planned regulatory scheme. This extension would allow the agency to first gather baseline impact data to the greatest extent possible before further defining the planned regulatory oversight scheme. After 48 years of regulatory discretion a few more months of very careful data gathering can only enhance the implementation of a meaningful regulatory transition, that by the FDA's own estimate could impact approximately 11,000 clinical laboratories, all those now authorized under CLIA to perform high complexity testing. We would encourage the FDA to first gather comprehensive data with respect to the types, numbers, locations, target populations and known analytical and clinical validity parameters of LDTs

currently in existence and being used. This would suggest an expanded data element list from the one currently suggested to be reported by each of the 11,000 high complexity laboratories now offering any LDT. Creating an interactive database to allow online reporting and agency review and analysis of this information is a critical step in this process. It must be noted that the Genetic Test Registry (GTR) operated by the National Center for Biotechnology Information/National Institutes of Health received reports of over 24,000 tests for 6,000 medical conditions involving over 3,600 human genes from laboratories in a voluntary informational database. Most if not all of these tests would be expected to be LDTs now reportable to FDA in order for any regulatory scheme to move forward. These represent only the genomic realm of LDT analytes and include none of the chemistry, hematological, or microbiological or other markers and analytes. The data elements to be collected might be modeled after GTR or other LDT oversight review systems such as the New York State Clinical Laboratory Evaluation Program (NYS CLEP). The list should include, in addition to those suggested by the FDA: indication of analytical validity; calculated clinical validity and citation to relevant literature for such claims; target populations; if a genetic test, germline or somatic cell target; name of analyte tested; suggested risk classification. Efforts should be made to leverage the CLIA oversight of the clinical laboratories to encourage (compel) every high complexity laboratory to comply with the data submission requirement over a reasonable time period of perhaps a year. For completeness of data gathering, any high complexity laboratory not currently offering any LDT would be required to submit a certification to that effect. Further leverage could be obtained by rewarding those laboratories submitting data in a timely and complete format with invitations to the stake holders meetings and access to technical assistance on a priority basis.

Following the gathering of this comprehensive data base, a series of public meetings with the stakeholders from the laboratory industry and the FDA can be used to consider proposals for recommendation for the classification scheme to prioritize regulatory review modalities and options. One issue seems to be the need for a much greater clarification about the criteria used to come up with classifications. This interactive process should occur before the regulatory oversight scheme is further developed.

2) CLIA Regulatory Oversight

CLIA and applicable regulations (42 C.F.R. Part 493) cover operational and performance standards for laboratories performing moderate to high complexity tests, such as LDTs. Under the CLIA regulations, the laboratory is already required to establish performance specifications to monitor, test and evaluate the overall quality of its analytic systems for accuracy, precision, analytical sensitivity and specificity, reportable range and reference intervals.

Section C(3) of the proposed guidance indicates that CLIA requirements address the laboratory's testing process (i.e., the ability to perform laboratory testing in an accurate and reliable manner), but do not assess the clinical validity of a LDT (i.e., the accuracy with which the test identifies, measures, or predicts the presence or absence of a clinical condition or predisposition in a patient). However, the FDA acknowledged that a

premarket review of clinical validity will not be required for certain LDTs (categorized as "lowest-risk") because of low potential of patient harm due to inaccurate LDT results. We contend that the CLIA regulations are appropriate oversight. The FDA should fully explore with its sister agency CMS the expansion and modernization of that existing system before creating a parallel but divergent additional regulatory oversight burden.

We are also concerned that a risk-based approach to stratify regulatory of LDTs does not adequately consider that harm to the patient may result from the treating/ordering practitioners' medical decisions informed by the LDT results, regardless of the performance of the test. It is the licensed treating professionals who are trained and responsible for making such medical decisions utilizing the research and medical information available. Based on the proposed guidance, the FDA appears to be concerned with acting as the decider of whether there is sufficient-evidence based rationale for the providers and patients to use the results of certain LDTs in making such medical decisions, or to practice medicine. We contend that questions remain as to whether this guidance exceeds FDA's oversight authority. In addition to this concern, below we highlight the specific technical issues which we believe to be the most important raised by the proposed guidance.

3) **Technical Aspects**: Develop further clear, specific, detailed guidance on technical aspects of any future intended regulatory oversight or guidance including:

A. Clinical validity. The draft guidance noted that clinical validity of a laboratory-developed test, which it defined as "the accuracy with which the test identifies, measures, or predicts the presence or absence of a clinical condition or predisposition in a patient," is not considered by the CLIA regulatory guidelines. The commonly used metrics for clinical validity are sensitivity, the ratio of true positives divided by all affecteds in the target population, and specificity, the ratio of true negatives divided by all unaffecteds in the same population. The test accuracy is also influenced by the prior probability of the condition. For a symptomatic person, this prior probability may be well in excess of 10%, whereas for a predisposition, it may be far less. For a seemingly excellent test with 99% sensitivity and 99% specificity, a clinical suspicion of disease, say 20%, would be elevated to 95% in a person who tested positive, essentially confirming the diagnosis. However, when the same test is an incidental finding in an otherwise healthy person for a condition with a population prevalence of 1/1000, the likelihood that the person had the disease would be only 9%, i.e. a false positive result. Thus, in order to create uniformity, greater consideration should be given to the threshold values of accuracy that would be indicative of clinical utility for the intended test applications. These threshold values should be applied not only to new studies in which the LDT developer is trying to measure clinical utility, but also for studies previously reported in the medical literature. Review of such previously reported clinical validities might well indicate a range of accuracies that were acceptable.

B. Bioinformatics as an intricate part of LDTs.

To what extent is bioinformatics analysis included in the LDT guidance and under which conditions? For example, in the area of genomic analysis there are software programs and laboratory information systems that create a great amount of data. In a genome of 3 billion base pairs there may be 3-4 million medically actionable variants identified. Certain software is used to create this data while separate software must be used to interpret the data, making complex computations. Such bioinformatics analysis may be done by (i) the same clinical lab as part of the LDT, (ii) the same clinical lab using a separate stand-alone software separate and apart from the "wet" lab portion of its activities, (iii) a third party clinical lab or (iv) a non-clinical lab using its own stand-alone software.

Where a clinical lab claims that its test both creates and interprets the data, such test would be an LDT by way of the definition of IVD under 21 CFR 809.3(a) which include "reagents, instruments and systems intended for use in the diagnosis of disease or other conditions, including a determination of the state of health, in order to cure, mitigate, treat or prevent disease…" (Emphasis added). If the bioinformatics analysis were separate from the LDT or done by a third-party, to what extent would the guidance regulate such bioinformatics analysis? If the bioinformatics were done in stand-alone software separate from any "wet" lab services, would such activity be an LDT under this guidance?

We note that while the FDA has exercised enforcement discretion in the past, it has made exceptions to its exercise of enforcement discretion when there was a perceived risk to the public. For example, with respect to "in vitro diagnostic multivariate index assays" (IVDMIA), FDA proposed a particular approach. In its 2007 draft guidance FDA asserted that IVDMIAs "do not fall within the scope of the LDTs over which FDA has generally exercised enforcement discretion" because they include "complex, unique interpretation functions," consisting of algorithms generally performed by software, that combine multiple sources of data to generate a classification or score correlating to a person's prognosis or risk of developing a disease. (See FDA, Draft Guidance for Industry, Clinical Laboratories, And FDA Staff: In Vitro Diagnostic Multivariate Index Assays (July 26, 2007).)

In the draft guidance the FDA stated that such tests "are developed based on observed correlations between multivariate data and clinical outcome, such that the clinical validity of the claims is not transparent to patients, laboratories, and clinicians who order these tests. Additionally, IVDMIAs frequently have a high risk intended use. FDA is concerned that patients are relying upon IVDMIAs with high risk intended uses to make critical healthcare decisions when FDA has not insured that the IVDMIA has been clinically validated and the healthcare practitioners are unable to clinically validate the tests themselves. Therefore, there is a need for FDA to regulate these devices to ensure that the IVDMIA is safe and effective or its intended use." (*Id.* page 4)

As this guidance in the case of the IVDMIA, where the computational analysis was part of the assay itself, was never fully implemented by the agency, does the LDT FDA guidance reach the other instances where the analysis is not an immediate part of the laboratory assay? The agency's published intent to consider Next Generation Sequencing Diagnostic Tests separately from the LDT guidance suggests multiple confusing pathways of regulatory oversight. This requires resolution before any plan can proceed.

C. Definition of Healthcare System and the Healthcare System Exclusion (Traditional LDTs)

In Section D(5) of the proposed guidance, the FDA has identified four factors it intends to consider in continuing to exercise enforcement discretion for premarket review and quality system requirements for the categories of tests called "Traditional LDTs." One such factor is related to the physical location and whether the LDT is both manufactured and used by a "healthcare facility" laboratory for a patient that is being diagnosed and/or treated at that same healthcare facility or within said facility's healthcare system. The proposed guidance defines the term "healthcare system" means "a collection of hospitals that are owned and operated by the same entity and that share access to patient care information for their patients, such as, but not limited to, drug order information, treatment and diagnosis information, and patient outcomes."

We contend that it is not justifiable to limit this factored analysis only to Traditional LDTs manufactured and used by a healthcare facility. The CLIA regulations make no distinction in the definition of a laboratory between an independent laboratory and hospital or physician based laboratory (42 C.F.R. § 493.2). The FDA's explanation for exercising enforcement of LDTs is the advent of increased risk to patients; however, the FDA offers no support for the contention that there is an inherent advantage to reducing such risk if a healthcare facility manufactures and uses an LDT. In giving deference to healthcare facility laboratories in this context, the FDA expressly states that it is the continued duty to treat the patient in the same healthcare facility, not the analytical and/or clinical validity of the LDTs, which supports the distinction. The FDA does not provide a substantive reason to suggest an independent laboratory could not similarly mitigate risks associated with Traditional LDTs if the other three factors were satisfied: (i) the device meets the definition of LDT; (ii) LDT is comprised only of components and instruments that are legally marketed for clinical use; and (iii) LDT is interpreted by qualified laboratory professionals, without the use of automated instrumentation or software for interpretation.

In conclusion, whether the diagnostic test is being performed in a laboratory that is independent of a healthcare delivery system should not, in turn, impact the level of risk associated with the analytical and/or clinical validation of the diagnostic test results.

D. Laboratory Test definition. A particular definition challenge arises for tests that involve genetic sequence analysis. Many diseases have heterogeneous causes, with mutations in several genes all constituting risk factors. These tests could involve sequencing single genes or all of the genes in a panel or a genome and then selecting a subset to analyze. This selection may be revised over time as new genes are identified as contributors and previously accepted are excluded. Thus, do single gene, gene panels and whole genomes (or exomes) constitute different tests or do they constitute the same test? Is genomic sequencing one test multiple tests determined by the ordering indication? What happens to tests over time as new discoveries are made that undermine their previously-accepted clinical validity? Can a test of higher complexity pre-empt a test of lower complexity, so that the low complexity test is deemed no longer clinically valid and, thus, should be discontinued? These concepts may not be specific to sequencing test, but may also be applicable to other multianalyte tests, where individual analytes and combinations of analytes may all be deemed to have clinical validity.

E. "Rare diseases" and "Unmet Need". Tests for rare diseases constitute a special class as these are subject to a Humanitarian Device Exemption from FDA oversight. These exemptions could create enormous loopholes; thus, who does the counting -- the laboratory, the FDA or a third party? For diseases that have heterogeneous causes, each cause may be rare, but the collective causes may not. Cases could be counted by symptomatic individuals or by positives results; however, positive results may not reflect true prevalence, due to non-specific test result or genetic non-penetrance. Tests that are performed more than 4,000 times per year fall out of the Humanitarian Device Exemption. Nonetheless, labs could create a loophole by having multiple versions of test, each of which would be performed less than 4,000 times per year. Thus, greater consideration needs to be considered for the case counting mechanism. Exemption of such tests may not be warranted as such conditions and single test sources may represent serious patient care risks.

Going forward, we believe that FDA should plan to exercise regulatory discretion for a longer period than anticipated in the framework, particularly for LDTs for rare diseases, and LDTs for unmet medical needs, even if FDA clears or approves an in vitro diagnostic (IVD) for the same intended use. The proposed FDA framework requires laboratories offering the same test for the same intended use to submit their own LDT as an IVD for premarket approval (PMA) within twelve months for continued regulatory discretion. If the FDA were to enforce PMA submission requirements on all of the laboratories that failed to submit PMAs within twelve months for the same IVD for the same intended use, the FDA would adversely affect the standard of care by removing LDTs that are superior to the first-approved IVD for that intended use. Particularly for LDTs developed for rare diseases or unmet needs, it may be difficult, if not impossible, for most laboratories to conduct the necessary clinical trials and submit a PMA in twelve months just because another laboratory did. And just because another laboratory submitted the first clearance or approval

does not mean that should be treated as superior or should be the standard of care for rare or unmet need products.

In this context, we believe that the FDA will likely need to consider oversight or pre-approval strategies for LDTs submitted as IVDs that utilize far fewer clinical tests than are often required for FDA's more rigorous standards such as PMAs. For example, many of the laboratories in the NYS CLEP program did not or could not conduct enough tests that would support a PMA yet may represent the appropriate standard of care for rare diseases or other diseases that have not been adequately characterized or treated. In these instances, as long as patients are receiving the appropriate standard of care by the LDTs currently being offered, we would suggest that the FDA should continue to exercise regulatory oversight rather than direct every laboratory to implement the first-approved IVD for a particular intended use. Such an approach would encourage innovation for IVDs rather than stifle it under a strict twelve-month submission requirement once the first IVD for an intended use is cleared or approved.

F. Analyte Specific Reagents . Analyte specific reagents as manufactured and sold by entities registered with the FDA as certified good manufacturing procedure vendors of reagents for development of clinical laboratory developed tests are in wide use in the clinical laboratory community. However under the ASR rule as issued by the FDA the information that such vendors can provide to the laboratory has been greatly limited. Although such ASRs are considered legal components of an LDT developed by a single laboratory, were that laboratory to be required to submit Premarket Approval documents to the FDA, or even an equivalency application under the "510(k)" alternative, the necessary technical information about the reagents used, the manufacturing process and other details would not generally be available to the laboratory for inclusion in such a submission. If the FDA intends to continue to pursue the oversight of LDTs developed using such ASR revisions to the "ASR rule," the level of communication between reagent manufacturer and the laboratory must be considered. Alternatively, for many ASRs where multiple laboratories purchase the same reagents from a single vendor and apply that reagent in a common methodology, to similar patient populations for detection of the same disease marker, the ASR itself might better be classified as an IVD and the manufacturer required to submit the necessary materials for clearance as such an IVD. Cooperation between labs and manufacturer would still be required to gather the necessary clinical performance data for the application of the ASR-based IVD. This would limit the review work volume to once per "ASR kit" rather than hundreds of submission from individual laboratories.

G. "Research Use Only" (RUOs). It is well known that "today LDTs are frequently manufactured with components and instruments that are not legally marketed for clinical use." Many of these products are labeled as "Research Use Only" by the manufacturer, often because that entity intends to avoid registration with the FDA completely or because they have not, or will not collect the necessary data

for the performance of the particular component or instrument or software. It is apparent that just as the FDA has exercised regulatory discretion with the clinical laboratories who have developed LDTs, the agency has also applied regulatory discretion in failing the proactively police the manufacturers of RUO-labeled components that are clearly used in clinical test development. If the use of such materials and instruments categorizes the lab developed test as an IVD, immediately implicating manufacturer registration, production quality requirements and IVD premarket approval or 510(k) submission requirements innovation in clinical laboratory medicine will suffer. Much as with ASRs, where multiple laboratories purchase the same research labeled components from a single vendor and apply those materials in a common methodology, to similar patient populations for detection of the same disease marker the manufactured component, instrument or software itself might better be classified as an IVD and the manufacturer required to submit the necessary materials for clearance as such an IVD. Cooperation between labs and manufacturer would still be required to gather the necessary clinical performance data for the application of the now RUO-based IVD. This would limit the review work volume to once per "RUO kit" rather than hundreds of submission from individual laboratories.

H. Contract Manufacturing. Laboratories have historically "contracted" with third parties for the routine manufacture of key components of their LDTs. If as stated, it is the goal of the proposed FDA regulatory oversight of such LDTs to assure quality, patient safety, and clinical efficacy, guidance which disrupts this contracting arrangement is counterproductive. Use of contract manufacturing of test components helps assure uniformity of the materials produced according to such contracts. Here there are not multiple laboratories using a single ASR or RUO component from a single manufacturer, but a single lab using a product manufactured according to contract specifications. It is appropriate that if LDTs are to be the subject of FDA regulatory oversight, then such tests using contract manufactured materials should be reviewed based on materials submitted by that individual laboratory. However, use of such manufacturing contracts should not alter the review process and timeline of LDT review.

We thank you for the opportunity to submit these comments and look forward to a continued discussion.

Submission by the New York State Bar Association Health Law Section Committee on Medical Research and Biotechnology (Committee Co-Chairs, Alex Brownstein and Sam Servello) and the Food, Drug and Cosmetic Law Section (Chair, Brian Malkin)