Update on Compounding for Animals

- Update on Compounding for Use in Animals
- Compounders versus Drug manufacturers
- Federal versus State authority
- Veterinary Board versus Pharmacy Board
- Food animals versus Companion Animals
- Other Extra label use

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- NJ State Board of Veterinary Medical Examiners
- NJVMA
- Clients: Animal-related industries from Pharma to farmers

Compounding

Client Handout

AVMA members: Provide individual clients with needed information about the compounded medications you prescribe, including when to contact you after returning home.

Compounding – any manipulation of an FDA-approved drug product beyond that stipulated on the product's label – is needed in veterinary medicine to provide individualized medication for specific patients with special needs not met by FDA-approved drug products. Manipulation might include mixing, diluting, concentrating, flavoring, or changing a drug's dosage form to accommodate a specific patient's needs.

Examples of compounding include:

- Mixing two injectable drugs
- Creating an oral suspension from crushed tablets or an injectable solution
- Adding flavoring to a commercially available drug

https://www.avma.org/KB/Resources/Reference/Pages/Compounding.aspx?PF=1

Importance of Veterinary Compounding

The AVMA and veterinarians believe that at least three circumstances exist wherein compounds prepared from bulk drug substances might be necessary:

1. the approved product is not commercially available, or
2. the needed compounded preparation cannot be made from the approved product, or
    a. approved formulations contain excipients that the patient may be allergic to.
    b. approved formulations come in strengths that may make dispensing to the patient difficult.
    c. approved formulations may contain sustained or extended release coating and therefore not be able to be used as a compounding formulation.
3. there is no approved product from which to compound the needed preparation.

Compounding of Animal Drugs-AVMA's comments to GFI # 230.

Importance of Veterinary Compounding

- “In species including but not limited to zoo animals, laboratory animals, exotic pets, wildlife, aquaria animals, and non-food aquacultural animals, the use of compounded preparations is unquestionably necessary.” AVMA’s comments to GFI # 230.

Importance of Veterinary Compounding

- United States population of 183.9 million dogs and cats owned by 107.3 million households (65%).
- Approximately 30-37% of all households in the U.S. own a total of 74-96 million cats.
- The U.S. equine industry involves 9.2 million horses owned by 2 million people, and more than 4.6 million Americans are directly involved in the equine industry, supporting 1.4 million jobs with an annual $102 billion impact on the U.S. economy (in 2014).

American Pet Products Association, Inc.'s 2017-2018 National Pet Owners Survey

Comments from American Association of Equine Practitioners to FDA Notice GFI #230

Veterinary Compounding Pharmacy Industry

- The global compounding pharmacies market is projected to expand at a Compound Annual Growth Rate (CAGR) of 6% during 2015-2021.
- Compounding pharmacies accounted for market revenue worth $6.5B in 2014 and the revenue is expected to increase to $9.75B by 2021.
- More than two thirds of global sales of compounded animal drugs will remain concentrated in the US and Canada. North America's animal drug compounding market is projected to witness revenue growth at 7% CAGR.
- FDA estimated that 75,000 pharmacies fill 6.35M compounded prescriptions for animals in the US each year.

Compounding Pharmacies Market Will Reach US $9.7B by 2021 – December 2017: NB Herald
Animal Drug Compounding Market to Reach $1.4B by 2024: April 2017: Persistence Market Research

Compounding of Animal Drugs- Is it Legal?

To be legally marketed, new animal drugs must be approved under section 512 of the FD&C Act, conditionally approved under section 571 of the FD&C Act, or included on the Index of Legally Marketed Unapproved New Animal Drugs for Minor Species under section 572 of the FD&C Act. The FD&C Act does not generally distinguish between compounding and other methods of animal drug manufacturing. Animal drugs that are not approved or indexed are considered "unsafe" under section 512(a)(1) of the FD&C and adulterated under section 501(a)(5) of the FD&C Act. Animal drugs compounded from bulk drug substances are new animal drugs.

https://www.fda.gov/AnimalVeterinary/ResourcesforYou/ucm268128.htm#Compounding_of_Animal_Drugs

Compounding in Animals from Bulk Substances- Is it illegal?

According to the AVMA, citing the FDA ,“[c]ompounding of drugs from unapproved (bulk) substances for use in animals is currently illegal under the Federal Food, Drug, and Cosmetic Act and the Animal Medicinal Drug Use Clarification Act.”

https://www.avma.org/KB/Policies/Pages/Compounding-from-Unapproved-Bulk-Substances-in-Food-Animals.aspx

Compounding in Animals from Bulk Substances- Is it illegal?

"We agree with FDA that the compounding of animal drugs from bulk drug substances results in new animal drugs that must comply with the FD&C Act's approval/indexing requirements. This fact has been upheld by every Federal Court of Appeals that has considered the issue." Comments from Animal Health Institute to FDA's GFI #230 (AHI is the US trade association for research-based manufacturers of animal health products.)

- AHI also cited to 2015 GAO report agreeing that animal drugs from bulk substances were new animal drugs. GAO-15-671, at p.2.

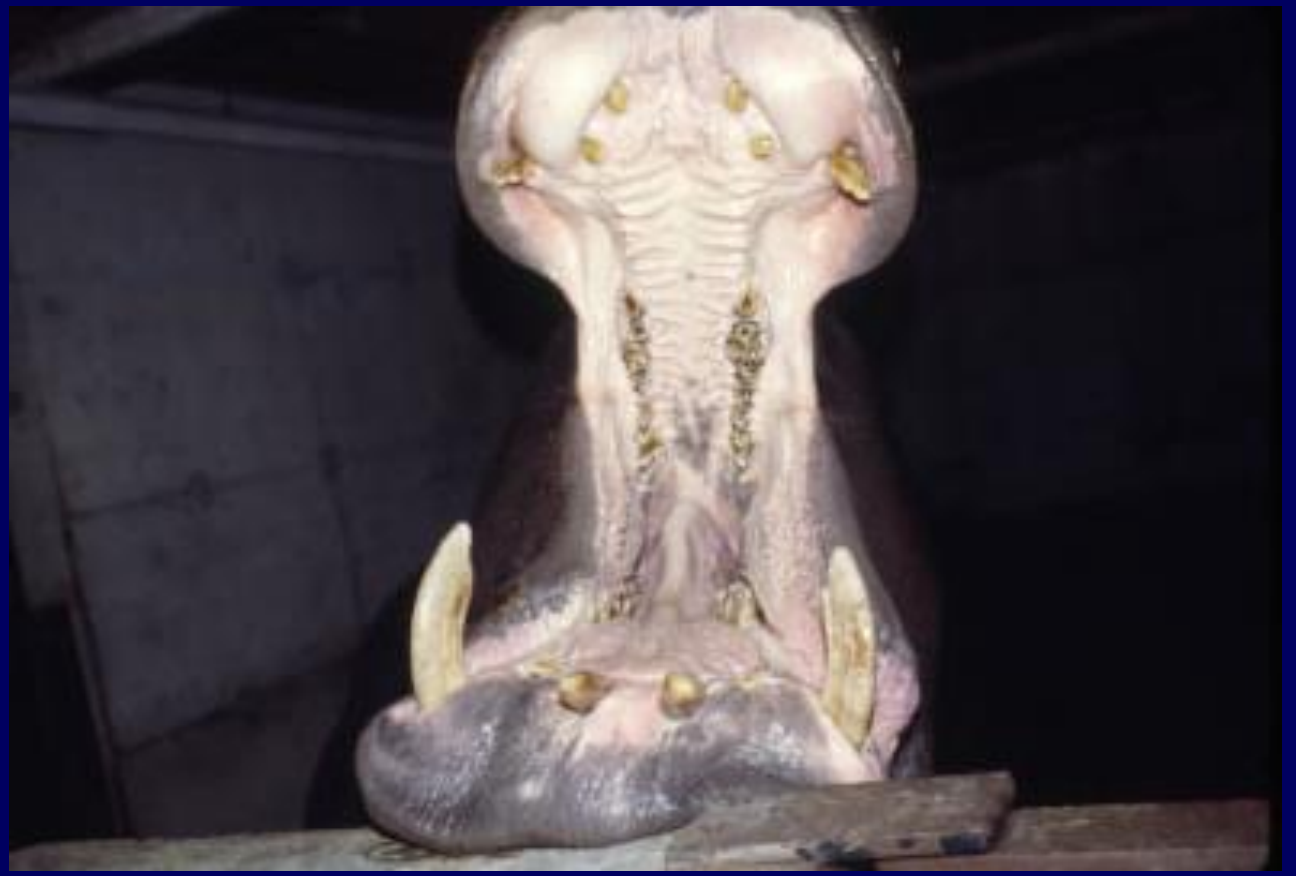
Compounding in Animals from Bulk Substances- Is it illegal?

"[T]he Government also acknowledges that 'because obtaining FDA approval for a new drug is a costly process, requiring FDA approval for all drug product compounded by pharmacies for the particular needs of an individual patient would, as a practical matter, eliminate the practice of compounding, and thereby eliminate availability of compounded drugs for those patients who have no alternative treatment.'" *United States v. Franck's Lab, Inc*., 816 F. Supp. 2d 1209, 1247 (M.D. Fla. 2011) (quoting Thompson v. W. States Med. Ctr., 535 U.S. 357, 369 (2002)).

Compounding in Animals from Bulk Substances- Is it illegal?

"Congress did not intend to give the FDA per se authority to enjoin the long-standing, widespread, state-regulated practices of pharmacists filling a veterinarian's prescription for a non food-producing animal by compounding from bulk substances." *United States v. Franck's Lab, Inc*., 816 F. Supp. 2d 1209 (M.D. Fla. 2011) (holding FDA was not authorized by Congress to enjoin a state-licensed pharmacist from engaging in the traditional practice of compounding animal drugs from bulk substances).

Does Extra Label Drug Use Permitted Pursuant to the Animal Medicinal Drug Use Clarification Act (AMDUCA) of 1994 Legalize Veterinary Compounding?



AMDUCA

(a) Extralabel use means actual use or intended use of a drug in an animal in a manner that is not in accordance with the approved labeling. This includes, but is not limited to, use in species not listed in the labeling, use for indications (disease or other conditions) not listed in the labeling, use at dosage levels, frequencies, or routes of administration other than those stated in the labeling, and deviation from the labeled withdrawal time based on these different uses. 21 CFR 530.3

AMDUCA

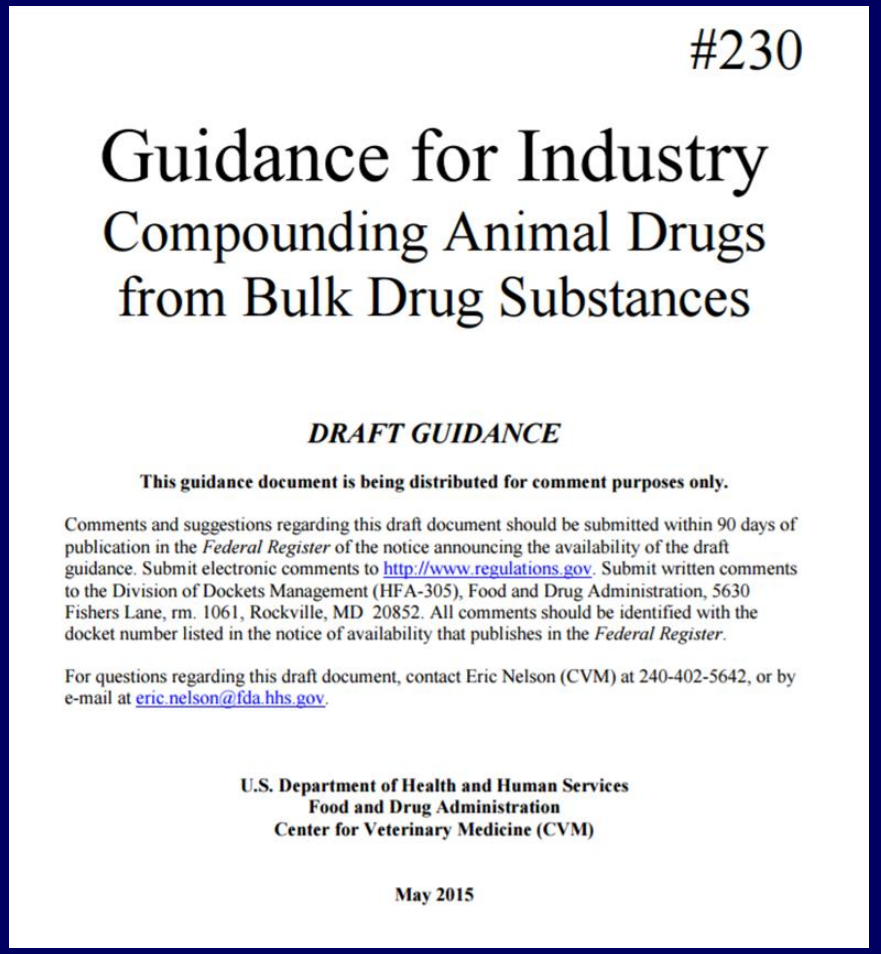
(a) This part applies to compounding of a product from approved animal or human drugs by a veterinarian or a pharmacist on the order of a veterinarian within the practice of veterinary medicine. Nothing in this part shall be construed as permitting compounding from bulk drugs. 21 CFR 530.13 (Extralabel use from compounding of approved new animal and approved drugs.)

Drug Quality and Security Act (DQSA) 2013

- As amended by DQSA, the FD&C Act provides two pathways for lawful compounding of drugs for humans under the Act.
  1. Under one pathway, in section 503A, state-licensed pharmacies, among others, compound drugs pursuant to patient-specific prescriptions (referred to as "503A facilities" or as "traditional compounders").
  2. Under the other pathway, in section 503B, drugs are compounded by a new category of compounders called outsourcing facilities (or "503B facilities") according to heightened statutory requirements relative to the 503A facilities.
- Drugs produced by outsourcing facilities must be compounded in compliance with current good manufacturing practice (CGMP) requirements and in an FDA-registered facility that is subject to regular, risk-based inspections.
- Not permitted to compound from materials deemed unsafe or not efficacious for humans.
- No resales.

GFI Facility Definition Under Section 503B of the Federal Food, Drug, and Cosmetic Act. April 2016. https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm166743.htm

Without similar authority for animal drug compounding, FDA included DQSA-requirements in its GFI #230. Withdrawn November 2017



#230

Guidance for Industry

Compounding Animal Drugs from Bulk Drug Substances

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to http://www.regulations.gov. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact Eric Nelson (CVM) at 240-402-5642, or by e-mail at eric.nelson@fda.hhs.gov.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Veterinary Medicine (CVM)

May 2015

Unsafe for Humans ≠ Unsafe for Animals

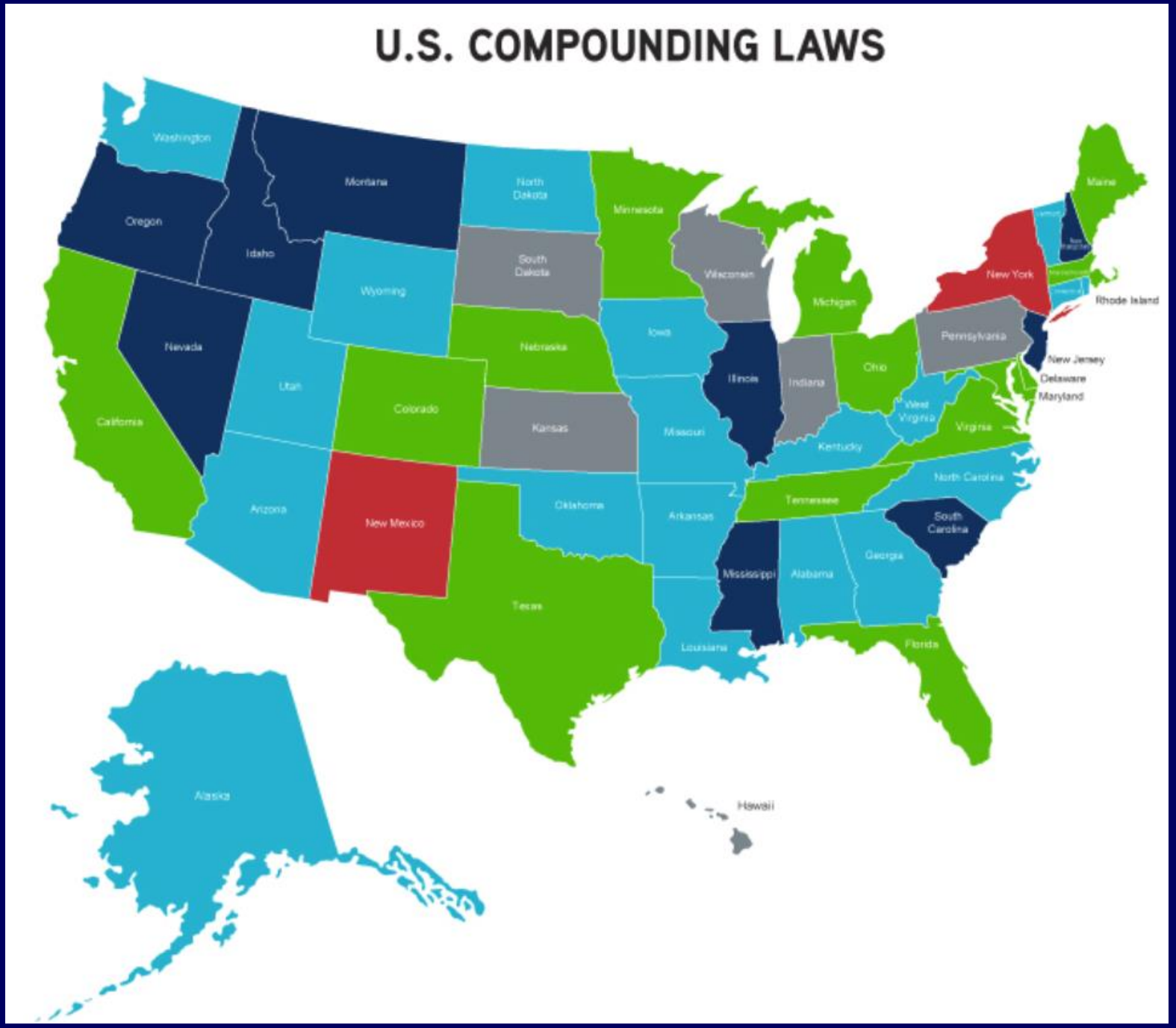
- An example of a commonly used bulk compounded drug in cats is cisapride which was taken off the market for humans many years ago due to safety concerns in people. However, it is a very effective colonic motility agent in cats and is used extensively by feline veterinarians.
- Another example-chloramphenical-treatment in horses, puppies.

Comments from American Association of Equine Practitioners, American Association of Feline Practitioners to FDA Notice GFI #230

Compounding of Animal Drugs- State versus Federal Authority

"The licensure of veterinarians is regulated by state governmental authorities. Given this is a federal guidance, not a regulation, coupled with the existence of a wide range of state compounding rules, we would appreciate clarification on how GFI #230 will be enforced by the FDA. State rules regulating compounding in veterinary practice vary greatly. Some even provide substantial permissiveness for veterinarians to obtain preparations compounded for office use, and administer and dispense from the compounded preparations maintained in their office."

AVMA's comments to GFI # 230.



Veterinarians may administer and dispense certain compounded products with some limitations.

Veterinarians may administer compounded products but it is unclear if dispensing is permitted.

Veterinarians may administer compounded products but dispensing and resale is prohibited.

Veterinarians prohibited from the use of compounded products for office use.

Laws on compounding for veterinary use not found.

https://www.avma.org/KB/Resources/Reference/PublishingImages/US-Map-Compounding-Laws.png

Animal Compounding in New York

Like the AVMA, the Board of Pharmacy has advised that New York does not permit compounding "for physician's office use" because it involves the dispensing of non-patient specific orders. It considers this type of activity to be "manufacturing." However, legislation adopted in 2014 requires that the label of any drug compounded by an outsourcing facility must include the statement that the drug is not for resale, and the statement "Office Use Only."

https://www.avma.org/Advocacy/StateAndLocal/Pages/compoundinglaws.aspx

Animal Compounding in New York- NYS Veterinary Medical Society

New York State law prohibits a veterinarian from reselling a compounded drug to a client/patient.

“Compounding pharmacies are advising NYSVMS that a veterinarian can order a compounded drug for a particular patient and administer it to the patient in-house, but may not charge the client/patient specifically for the drug . . .[because] any itemized charge for this drug on the bill . . .can be viewed as "reselling” the drug.

Animal Compounding in New York
137 NYSED §6807. Exempt persons.
Vet can prescribe

1. This article shall not be construed to affect or prevent:

. . .

b. Any physician, dentist, veterinarian . . . legally authorized to prescribe drugs under this title who is not the owner of a pharmacy, or registered store, or who is not in the employ of such owner, from supplying his patients with such drugs as the . . . veterinarian . . . legally authorized to prescribe drugs under this title deems proper in connection with his practice, provided, however, that all such drugs shall be dispensed in a container labeled with the name and address of the dispenser and patient, directions for use, and date of delivery, and in addition, such drug shall bear a label containing the proprietary or brand name of the drug and, if applicable, the strength of the contents, unless the person issuing the prescription specifically states on the prescription in his own handwriting, that the name of the drug and the strength thereof should not appear on the label; provided further that if such drugs are controlled substances, they shall be dispensed pursuant to the requirements of article thirty-three of the public health law;

Animal Compounding in New York
NYSED 137 §6807. Exempt persons.
Vet can dispense for 72 hour supply.

2. a. Notwithstanding the provisions of paragraph b of subdivision one of this section, no prescriber who is not the owner of a pharmacy, or registered store, or who is not in the employ of such owner, may dispense more than a seventy-two hour supply of drugs, except for:

. . .

2. the dispensing of drugs at no charge to their patients;

. . .

7. the dispensing of drugs that are diluted, reconstituted or compounded by a prescriber . . .

Animal Compounding in New York
137 NYSED §6802. Definitions.

1. "Pharmacy“ means any place in which drugs, prescriptions or poisons are possessed for the purpose of compounding, preserving, dispensing or retailing, or in which drugs, prescriptions or poisons are compounded, preserved, dispensed or retailed, or in which such drugs, prescriptions or poisons are by advertising or otherwise offered for sale at retail.
2. "Compounding" means the combining, admixing, mixing, diluting, pooling, reconstituting, or otherwise altering of a drug or bulk drug substance to create a drug with respect to an outsourcing facility under section 503B of the Federal Food, Drug and Cosmetic Act and further defined in this section.

Animal Compounding in New York
§6831. Special provisions - outsourcing facilities.

7. Bulk drugs. A drug may only be compounded in an outsourcing facility that does not compound using bulk drug substances as defined in section 207.3(a)(4) of title 21 of the code of federal regulations or any successor regulation unless:

a. the bulk drug substance appears on a list established by the secretary of health and human services identifying bulk drug substances for which there is a clinical need;

b. the drug is compounded from a bulk drug substance that appears on the federal drug shortage list in effect at the time of compounding, distributing, and dispensing;

c. if an applicable monograph exists under the United States Pharmacopeia, the national formulary, or another compendium or pharmacopeia recognized by the secretary of health and human services and the bulk drug substances each comply with the monograph;

d. the bulk drug substances are each manufactured by an establishment that is registered with the federal government.

Animal Compounding in New York

9. Unsafe or ineffective drugs. No outsourcing facility may compound a drug that appears on a list published by the secretary of health and human services that has been withdrawn or removed from the market because such drugs or components of such drugs have been found to be unsafe or not effective.

10. Prohibition on wholesaling. No compounded drug will be sold or transferred by any entity other than the outsourcing facility that compounded such drug. This does not prohibit the administration of a drug in a health care setting or dispensing a drug pursuant to a properly executed prescription.

11. Prohibition against copying an approved drug. No outsourcing facility may compound a drug that is essentially a copy of one or more approved drugs.

Office supply requirement for emergencies - compounded from bulk substances not on FDA list

- Acetylcysteine to treat acetaminophen & xylitol toxicity in cats & dogs.
- Ammonium molybdate to treat copper poisoning in sheep.
- Calcium EDTA to treat lead poisoning in cats, dogs, rabbits, birds, small mammals, & horses.
- Methylene Blue to treat methemoglobinemia in dogs, cats, ruminants, & horses.
- Physostigmine to treat ivermectin toxicity in dogs, and tall larkspur poisoning in cattle.
- Apomorphine to induce vomiting.
- Doxycycline for Salmon poisoning in dogs (commonly seen in Oregon).

Comments from Veterinarians to FDA Notice GFI #230

Concerns about provisions related to "Clinical difference"

"If the drug contains a bulk drug substance that is a component of any marketed FDA approved animal or human drug:

a. there is a change between the compounded drug and the comparable FDA approved animal or human drug made for an individually identified animal patient that produces a clinical difference for that individually identified animal patient, as determined by the veterinarian prescribing the compounded drug for his/her patient under his/her care . . ."

- Ambiguous.
- Requires drug testing for each use.
- Need for compounding not always based on clinical difference, but ability to treat. [pilling cats, especially lions].

Compounding related to High Cost

- Ophthalmic fungal medications – only one approved product, and according to veterinary ophthalmologist commenting, the cost was prohibitive for many clients (over $500/15 ml).
- Prednisolone, a drug that is commonly used in feline medicine. Generic prednisolone (approximately $.03 per 5 mg. tablet) went off the market some 2-3 years ago. The branded version, Millipred, has been periodically unavailable, and also cost-prohibitive for many clients ($5- $6.50 per 5 mg. tablet). Dosage may require several tablets per day.

Comments from Veterinarians to FDA Notice GFI #230

Population not individual treatment

- Concerns about impact to shelter veterinarians or those treating feral cat populations where “individually identified animal” is not possible.
- Similar concerns for treating herds, flocks, schools of animals.
- Issue involving food animals should be revisted-oral fluids, treatment for toxic exposure, depopulation.

Comments from American Association of Feline Practitioners to FDA Notice GFI #230

General Concerns-Vets cannot properly treat animals and animals will unnecessarily suffer without compounding from bulk substances

- Requirement for veterinarians to justify treatment is not required of other medical professionals who write prescriptions.
- Labeling requirements (“there are no FDA-approved animal or human drugs that can be used as labeled . . ”) not required for compounded medications for humans.
- All 50 states allow veterinarians to dispense FDA-approved drugs. Why should a patient have to suffer just because their special needs cannot be met by a manufactured drug?

General Concerns

"If the FDA's position is correct, Congress intended to give the agency the authority to require traditionally compounded medications for non food-producing animals to go through the FDA's lengthy and involved new drug approval process but declined to require it for compounded medications prescribed for human beings. This is simply too much for a public health statute like the FDCA to bear." *United States v. Franck's Lab, Inc*., 816 F. Supp. 2d 1209, 1250 (M.D. Fla. 2011).

Questions?

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