New York State Bar Association
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COMMENTS SUBMITTED ON BEHALF OF THE FOOD, DRUG AND COSMETIC LAW SECTION on U.S. Food and Drug Administration (FDA) Draft Guidance No. 230 Entitled "Guidance of Industry Compounding Animal Drugs from Bulk Drug Substances- Docket No. FDA–2015–D–1176

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As members of the New York State Bar Association Food, Drug and Cosmetic Law Section, we are pleased to offer these comments on the U.S. Food and Drug Administration (FDA) Draft Guidance No. 230 entitled "Guidance of Industry Compounding Animal Drugs from Bulk Drug Substances" issued in May 2015 (hereinafter, "Draft Guidance"). We applaud FDA's efforts to improve the safety, efficacy and reliability of bulk compounded drugs in the animal health arena and FDA's efforts here to provide a more nuanced guidance on issues related to bulk compounding for animals in view of the Federal Food, Drug and Cosmetic Act ("FD&C Act") and FDA's related statutory authority.[1]

As an initial matter, we encourage FDA to consider initiating notice-and-comment rulemaking for establishing guidelines for permissible bulk compounded animal drugs rather than relying on a more informal draft-to-final guidance procedure that it appears to have currently chosen. Use of bulk drugs in compounding is an important issue in animal health requiring a more formal and complete engagement of both the public and the diverse stakeholders in animal health that would help ensure any final rules or guidance meet the goals of improved safety and reliability of bulk compounded drugs while not limiting access to important treatment options for those working in animal health. As Congress realized when it decided not to include animal drug compounding in the Drug Quality & Security Act, in particular the concept of outsourcing pharmacies,[2] animal

[1] FDA's position that all animal drugs compounded from bulk drug substances are unapproved animal drugs and therefore adulterated under the FD&C Act was recently called into question by *United States v. Franck's Lab, Inc.*, 816 F. Supp. 2d 1209 (M.D. Fl. 2011) (holding that in FDA's first case to enjoin a state-licensed pharmacist from engaging in the traditional practice of bulk compounding animal drugs, "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"). While this case was initially appealed by FDA, it was later jointly dismissed as moot. Among other things, this Draft Guidance seeks to articulate enforcement discretion for state-licensed pharmacies or veterinarians compounding animal drugs from bulk drug substances for non-food animals and develops a new framework for outsourcing facilities that compound animal drugs similar to the one developed for the compounding of human drugs in the Drug Quality & Security Act (Pl. 11-2013).

[2] *See* S.959, Pharmaceutical Quality, Security, and Accountability Act (introduced May 15, 2013).

health issues differ in many ways from human health issues. There are a variety of different stakeholders and consumers in animal health that could provide FDA with useful insights on the many issues surrounding the compounding of bulk drugs for use in animals, including veterinarians, animal and human pharmacies and pharmacists, food animal workers, caretakers in zoos, aquariums, ornamental animal, and wildlife refuges, companion animal owners, researchers using laboratory animals, handlers of service animals and law enforcement animals, and sport and performance animal trainers, to name a few. Taking advantage of the knowledge and perspectives of these stakeholders would greatly benefit the final rules that FDA issued. In addition, going through the formal rule making process would also be a more appropriate format, since Congress had not spoken yet on the issue of compounding bulk substances for animal health, which was also a contentious issue for human drug compounding. The Animal Health Law Committee is here to help and to offer its assistance to FDA on this issue in any public setting FDA chooses.

Comments on Draft Guidance

To the extent FDA decides to issue final guidance based on this Draft Guidance, we support the American Veterinary Medical Association's (AVMA) Comments (hereinafter, "AVMA's Comments") in general, which we have reviewed in advance of our comments, submitted in response to this same Draft Guidance and further emphasize aspects of and supplement the AVMA's Comments as provided below. Section references refer to the Draft Guidance unless otherwise noted.

We would like to highlight the following key issues and concerns with the Draft Guidance, many of which are discussed more fully below or in the AVMA's Comments:

1. There are a number of undefined terms that should be clarified to allow for compounding entities to successfully comply with the Draft Guidance. (*See* Clarification and Definitions discussion below.)

2. Veterinarians do not always have the ability or desire for various reasons to compound drugs themselves in their practices but do have a regular need for certain bulk compounded drugs. Veterinarians therefore need to be able to not only administer such drugs themselves directly to a patient but also provide such drugs to clients for administration to patients at home. (*See* Administrate and Dispense definition discussion below; *see* Sections III.A.9, III.B. 5 & 7, III.C.6.)

3. The collection of only severe adverse events (*see* Sections III.A.10., III.B.8., III.C.7.) is not only ambiguous as to what adverse event would qualify as severe but, by limiting the collection to only certain types of adverse events, the usefulness of collecting adverse event information at all could be reduced. (*See* Severe Adverse Event definition discussion below and AVMA's Comments.)

   Further, we agree with the AVMA that the submission of adverse events in animals should be modernized and streamlined with a digital submission system instead of via paper Form FDA1932a. This would not only ease the burden on smaller practitioners in submitting such forms, but, hopefully, allow access and analysis of adverse event information more expediently so as to identify any potential problems more quickly. (*See* AVMA's Comments.)

4. The complete ban on the use of any bulk compounded drugs in food animals would be too restrictive and should be reconsidered in view of public health and emergency considerations. (*See* Sections III.A.3., III.B.2. and III.C.3; *see* Food Animal discussion below.)

5. The current limitation to compounding only for a single, individually identified patient is not practical for the realities of veterinary practice. (*See* Sections III.A.2, III.B.1.) We believe the AVMA's definition for "patient" should be adopted throughout the Draft Guidance instead. (*See* AVMA's Comments.)

6. There are a number of instances in the Draft Guidance where specific statements are required to be written on a prescription or label that has limited space. We propose instead a shorter statement used in all such instances that refers back to the appropriate regulation or guidance – "In accord with FDA Guidance # 230," for example. (*See* Sections III.A.3, 4, 6, III.B.2., III.C.3, 9.) For statements regarding food animals, we propose including "Prepared from bulk substance – not for food animals" on the label instead of the current statements. (*See* Sections III.A.3, III.C.3.) If FDA allows some bulk compounded drugs to be used in food animals, the statement should be altered accordingly to, for instance, "Warning for Food Animals: Prepared from bulk substance."

7. Finally, we believe FDA should consider broadening a veterinarian's discretion beyond the requirement that an approved animal or human drug or extra label use of such a drug always be used instead of an option that is compounded from bulk drug. (*See* Sections III.A.4., 6., III.B.3-4; *see also* Change and Clinical Difference and Veterinary Discretion discussions below.)

Clarifications and Definitions

As an initial matter, the following terms used throughout the Draft Guidance should be more clearly defined to reduce ambiguity and allow for successful compliance by compounding entities.

15 days. Sections III.A.10, III.B.8, and III.C.7. require that adverse events be reported on Form FDA1932a within 15 days. We ask that FDA clarify this to be 15 business days to reduce ambiguity and to account for non-working days such as weekends and national holidays.

Administrate and **Dispense**. These two terms both appear in Section III.B.7., which implies that ***administration*** is the giving of the compounded drug to a patient by the veterinarian in the practice while ***dispensing*** is when the veterinarian gives the compounded drug to the client to ***administer*** to the patient at home. Sections III.A.9. and III.C.6., however, only exclude "the administration of a compounded drug by a veterinarian to a patient under his or her care" from the ban on selling or transferring the compounded drug.

- First, it is unclear if "administration . . . to a patient under his or her care," can include administration by the client to the patient as directed by the veterinarian or not. Therefore the meaning of administration as well as dispense should be

made clear for purposes of the Draft Guidance. We would suggest the following definitions:

> *Administration*: "For purposes of this guidance, the terms administration or administer to a patient include both (1) when a veterinarian or an agent of the veterinarian, such as a veterinary technician, administers the drug to the patient (e.g., by injection or intravenously) and (2) when the veterinarian or their agent provides the drug to the owner to administer to the patient while under the veterinarian's or their agent's direct supervision (e.g., the veterinarian hands the owner the drug for the patient to take before leaving the veterinarian's office)."
>
> *Dispense*: "Dispense to patients means the act of delivering a prescription drug to an owner of the patient either:
> (1) By a veterinarian or an agent of a veterinarian, either directly or indirectly, for administration by the owner to the patient, outside the veterinarian's or their agent's direct supervision; or
> (2) By an authorized dispenser or an agent of an authorized dispenser under a lawful prescription of a veterinarian."

- Second, if "administration" in the Draft Guidance does not include a veterinarian dispensing the compounded drug to a client for administration at home, including if FDA adopts our proposed definitions, we believe FDA should consider altering the Draft Guidance to allow for veterinarians to administer and/or dispense bulk compounded drugs to their patients in both Sections III.A.9 and III.C.6. (*See also* AVMA's Comments.) For instance, home care may be a better or even the only option for a patient. Whether a veterinarian is unable to compound for some reason (e.g., inability to obtain an active ingredient, especially in a small amount for a single patient or cannot meet USP requirements) or prefers not to compound drugs him or herself, the veterinarian should still be able to have access to bulk compounded drugs that he or she can dispense for a patient under his or her care to clients for home administration to the patient. Also, many veterinarians prefer bulk compounded drugs to be sent to them directly, so that they can have the client come in for more detailed instructions on how to administer the drug at home to the patient. The inability of a veterinarian to dispense drugs to a client for administration to a patient that was ordered from a state-licensed pharmacy or an outsourcing facility would make this impossible.

- Third, Section III.B.8., appears to only allow a veterinarian to administer or dispense a bulk compounded drug to a patient when that specific veterinarian did the compounding. Many veterinarians, however, work in multiple doctor practice groups or hospitals where one veterinarian might do all or the majority of the compounding for all of the veterinarians in the practice. Also, it is possible that only one location for a multi-office practice will meet the USP Guidelines for compounding as required by Section III.B.5. As discussed by in the AVMA's Comments, these types of situations should be recognized and both administration and dispensing of these bulk compounded drugs allowed by the Draft Guidance and as provided in our suggested definitions.

Individually Identified Animal Patient. We agree with the AVMA that this definition (*see* Sections III.A.2, III.B.1.) is too narrow for the realities of the practice of veterinary medicine and support the adoption of the AVMA's definition of "patient" provided in their comments. (*See* AVMA's Comments.)

Food-Producing Animals. This term should be more exactly defined. We would suggest, for example, adding the following to Section III.A.3.: "A food-producing animal is any animal that produces food for human consumption, i.e. meat, offal, milk, and eggs. For purposes of this Draft Guidance, all cattle, swine, chicken, turkeys, sheep, goats, and non-ornamental fish are always considered to be food-producing animals . . . ."

Severe Adverse Event. Instead of the proposed requirement in the Draft Guidance for reporting only serious adverse events, we agree with the AVMA that all adverse events should be reported. To the extent FDA decides to keep a more limited requirement for adverse event reporting (*see* Sections III.A.10., III.B.8., III.C.7.), we encourage FDA to more clearly define the scope of adverse events that must be reported to allow for compounding entities and veterinarians to successfully comply with the Draft Guidance.

A Component of Any Marketed FDA-Approved Animal or Human Drug. It appears from this term's use in Section III.A.4. of the Draft Guidance that "a component of any marketed FDA-Approved Animal or Human Drug" means something different than "active ingredient." We suggest replacing this term with active ingredient, a term that is both already defined in the Draft Guidance at footnote 2 as well as easily understood and applied in the context of this Draft Guidance.

Change and **Clinical Difference**.

- **Change**. The Draft Guidance requires that "there is a change between the compounded drug and the comparable FDA-approved animal or human drug." (*See* Sections III.A.4., III.B.3.)

- **Clinical Difference**. The Draft Guidance further requires that this ***change*** produce a "clinical difference" for the patient. (Sections III.A.4.a. & b., III.B.3.)

- This language, appearing in Sections III.A.4. and III.B.3., seems to require a veterinarian know a clinical difference will be produced prior to prescribing or treating an animal with a bulk compounded drug instead of an FDA-approved animal or human drug option. Because it might not be possible to know a "clinical difference" will be produced, the veterinarian's reasonable judgment should govern. We therefore suggest the standard for prescribing a bulk compounded drug instead of an FDA-approved animal or human drug should be that the veterinarian "expects a clinical difference." (*Also see* the Veterinarian Discretion discussion below.) In addition, this language does not account for times when a FDA approved drug is unavailable for various reasons, such as drug shortages or discontinuation by the manufacturer. In such instances where a FDA approved drug is not available, bulk drug compounding should also be allowed. (*See* AVMA's Comments.)

Cannot Be Made. It is unclear how a state-licensed pharmacy will determine it cannot make a compounded drug from an FDA-approved drug in Section III.A.5. For instance, would a state-licensed pharmacy be required to attempt to extract and purify, possibly unsuccessfully or at least inconsistently, the active ingredient from the filler components of a dosage form, before it could compound, e.g., a liquid formulation from bulk active pharmaceutical ingredient(s)? As with the previous comment, we would suggest that the standard for a state-license pharmacy to select bulk active pharmaceutical ingredient(s) over those found in an FDA-approved animal or human drug should be that the state-licensed pharmacy "expects that the prescribed drug product cannot be made or would be made more consistently or safely with bulk substance than by compounding an FDA-approved animal or human drug." (*See* Veterinarian Discretion discussion below.)

- Also, for further efficiency and safety, FDA should add that for any drug listed in Appendix A, the state-licensed pharmacy does not have to make or document such a determination that it cannot be made from an FDA-approved animal or human drug.

Documentation. There are multiple places the Draft Guidance requires that something be documented – Sections III.A.3-6. We recommend that FDA provide more detail what kind of documentation would be sufficient (e.g., for Section III.A.5., is individual documentation for each prescription required or would a single document for all prescriptions for a specific bulk compounded drug be acceptable) and how long such documentation needs to be maintained to avoid incomplete or overly-burdensome record keeping over time.

Veterinarian Discretion

The Draft Guidance should permit veterinarians to prescribe bulk compounded drugs when the bulk compounded drug would enhance patient compliance and/or efficacy of treatment rather than the requirement appearing in Sections III.A.5, 6 and III.B.3-4 that an approved animal or human drug or extra label use of such a drug always be used instead of an option that is compounded from bulk drug. (*See* Sections III.A.5., 6., III.B.3-4.) For instance, a veterinarian's knowledge of a particular patient might inform him or her that this patient is too difficult for the owner to administer a tablet or capsule and therefore a liquid formulation, compoundable only from bulk drug, would be required for successful and efficacious treatment. An example of such a patient might be a fractious cat that refuses to swallow a pill but will take a liquid formulation, improving compliance. Or there are situations when a drug that is currently available only in bulk form, for instance due to a shortage or product discontinuation by the manufacturer, would be a better treatment option for medical reasons, such as improved efficacy or reduced side effects, than a different FDA-approved animal or human drug for the same indication. In such limited instances, for the benefit of the animal patient, a veterinarian should be able to prescribe bulk compounded drugs.

Food Animals

We understand that there are additional concerns with the use of bulk compounded drugs in food animals since any potential residues remaining from bulk compounded drugs could enter the human food supply. The complete ban against any bulk compounded drugs, however, removes treatment options, for instance, when there is a need for a poison antidote or depopulation medication. Here in particular, engaging in a discussion with the food animal stakeholders would

more fully probe the issues, where less restrictive options than a complete ban could be explored and developed. In fact, with the additional concerns related to Food Animals, a separate guidance might be more appropriate.

Pre-Production Compounding

In Section III.A.2., the limitations on pre-production compounding from bulk drugs for animals appears both unnecessary and may have negative public health effects. First, this restriction appears unnecessary, because state-licensed pharmacies are only able to sell animal drugs compounded from bulk drug in response to a specific, individual prescription, and such compounding entities would not want to have more bulk compounded drug then they would be able to sell. Further, and more importantly, in the case of a sudden shortage or outbreak where a bulk compounded drug would be an important treatment option, state-licensed pharmacies would be prevented from ramping up their production to meet the sudden increased demand by this requirement. This limitation on production would therefore potentially increase the spread of a disease and/or slow the rate of treatment, potentially causing a negative public health effect.

Outsourcing Facilities

In addition to the concerns discussed in AVMA's Comments regarding outsourcing facilities, we would add that, since there are not any animal drug outsourcing facilities currently registered, FDA should consider how many, if any, entities apply to register as outsourcing facilities for animal drugs. If few to no entities are interested in registering as outsourcing facilities for animal drugs, the use of state-licensed pharmacies to meet demand for bulk compounded animal drugs needs to be recognized by FDA and any final guidance issued from this Draft Guidance should be reconsidered and updated accordingly so as to ensure adequate access to bulk compounded drugs for animal patients.

Appendix A

Limiting outsourcing facilities to only the drugs listed in Appendix A for the species and conditions has the potential to perpetuate a drug shortage and the nomination and updating process requires further clarification. Under the Draft Guidance, only outsourcing facilities could ramp up production if needed, for instance, for a shortage or discontinuation or outbreak. In addition, Appendix A currently only provides for "review [of] the nominated bulk drug substances on a rolling basis and to periodically update this Appendix." FDA should explain the process for nominating a drug to be added to Appendix A and the updating the list periodically.

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

Submission by the New York State Bar Association Food, Drug and Cosmetic Law Section (Chair, Brian Malkin) (Animal Health Law Committee Co-Chairs, Brian Malkin and Magdalena Hale Spencer).