February 3, 2020

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

RE: Docket No. FDA-2018-D-4533; Compounding Animal Drugs From Bulk Drug Substances; Draft Guidance for Industry; Availability

Mr. Eric Nelson
Director, Division of Compliance (HFV-230)
Center for Veterinary Medicine
Food and Drug Administration
7519 Standish Pl.
Rockville, MD 20855

Dear Mr. Nelson:

The American Veterinary Medical Association respectfully requests ***at least*** a 120-day extension to the comment period for Docket ID: FDA-2018-D-4533; Compounding Animal Drugs From Bulk Drug Substances; Draft Guidance for Industry; Availability.

Since the release of draft Guidance for Industry (GFI) #256, Compounding Animal Drugs from Bulk Drug Substances, the AVMA has been actively seeking feedback from its members and other veterinary associations. The responses we have received indicate there are several areas of draft GFI # 256 where further information is needed to gauge the impact of the draft guidance on the veterinary profession. Two broad areas of confusion include the intersections of draft GFI # 256 with USP chapters and monographs and its interpretation in the context of existing CVM Compliance Policy Guides (CPG).

<u>Draft GFI # 256 and USP Chapters and Monographs</u>
With respect to the intersections between draft GFI #256 and USP Chapters, see for example, page 9, paragraph 2, subsection A of section III, Policy, which addresses compounding pursuant to patient-specific prescriptions for non-food producing animals. Draft GFI # 256 states:

> *"The drug is compounded in accordance with the current United States Pharmacopeia and National Formulary (USP-NF) Chapters <795> "Pharmaceutical Compounding – Nonsterile Preparations" or <797> "Pharmaceutical Compounding-Sterile Preparations" and complies with the standards of all applicable USP-NF monographs (e.g., a monograph for a bulk drug substance or a monograph for a compounded finished product)."*

Paragraph 3, subsection B of section III, Policy, which refers to compounding without patient-specific prescriptions (office stock) for non-food-producing animals, also references USP <795> and <797>.

The USP has excluded some activities from the scope of USP <795> and <797>[1]; has conducted hearings on appeals of USP <795>, <797>, and <825> on January 21-22, 2020; and has agreed to consider the AVMA's request that a veterinary-specific compounding chapter be developed. The AVMA hopes to hear from USP in May 2020 as to whether USP will or will not develop a veterinary-specific chapter.

Although the current USP standards technically remain applicable, until the status of the recently proposed revisions to USP <795> and <797> (and <825>) is resolved and the decision is made to develop, or not, a veterinary-specific chapter, it is difficult to determine the scope of questions and concerns that veterinarians may have about draft GFI # 256.

As a practical illustration of needed clarity, suppose doxorubicin is diluted into a bag of fluids to be administered intravenously and the addition of doxorubicin does not occur in an allowable primary engineering control (PEC; e.g., a type-2 biosafety cabinet) or that the PEC is not inside the allowable secondary engineering control (e.g., cleanroom suite or segregated compounding area, depending on how long it will be before the dose is administered to the patient). Because such a dilution is technically not compliant with USP <800>, does that mean the dilution is also not compliant with USP <797> (irrespective of the 4-hour timeframe) and, consequently, not compliant with draft GFI #256 ?

Draft GFI # 256 also includes language stating: "… *and complies with the standards of all applicable USP-NF monographs* …" In the absence of a published USP-NF monograph, is compliance with a monograph not required? Correspondingly, when a notice of intent to revise a published monograph is provided, is compliance with the unrevised published monograph required?

Draft GFI # 256 and CPG

Other questions posed by veterinarians about draft GFI #256 point to a need for more information about the relationship between draft GFI #256 and existing CPG.

Articles used for euthanasia and depopulation

Draft GFI # 256 appears to allow compounding from bulk drug substances for food-producing animals only in the case of antidotes used to treat toxicoses (page 12, subparagraph C, section III, Policy). The AVMA believes it is also appropriate and necessary to permit the use of compounded drugs for euthanasia and depopulation of food-producing animals. The AVMA published its 2020 interim update of the AVMA Guidelines for the Euthanasia of Animals on January 15, 2020. That document references drugs that may be impacted by draft GFI #256, as does the AVMA Guidelines for the Depopulation of Animals that were published in 2019. As written, the scope of draft GFI # 256 does not appear to include euthanasia of a food-producing animal for welfare reasons (e.g., pain, suffering) or depopulation of a herd or flock due to the presence of a notifiable disease, using a drug referenced in the AVMA's euthanasia or depopulation guidance, and in compliance with FDA CPGs 608.300 and 650.100.

Immobilization

Draft GFI # 256 shares the FDA's concerns regarding human and animal safety. With that in mind, we recognize that an animal drug may be needed immediately and that the time required to compound a drug in response to an individual patient prescription may result in animal injury or suffering, or human injury.

CPG 608.300 conveys the FDA's policy regarding the use of drugs for animal capture by animal control

[1] As an example, preparation of a single dose for a single patient for administration within 4 hours is not required to meet the standards in USP <797>.

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agencies. Immobilization of animals in zoos, wildlife rehabilitation clinics, and other similar settings is required not only to address animal safety and suffering, but also for human safety when caring for animals.

Although many minor species for which drugs may be needed for immobilization or capture are not food-producing species, some members of some species may be bred, cultured, farmed, ranched, hunted, caught, trapped, or otherwise harvested for the purpose of having the animals, or edible products from the animals, commercially distributed for consumption by humans or other food-producing animals in the United States consistent with FDA's definition of food-producing minor species. As written, the scope of draft GFI # 256 does not appear to include drugs used for capture or immobilization of food-producing minor species, and it is unclear whether such drugs intended for use in non-food producing animals would fall under the category of "patient specific" or "office stock."

Large-volume parenterals
Large-volume parenterals (LVP) are aqueous solutions typically used to provide fluid replacement therapy for animals, including during surgical procedures. In addition, sterile injectable drugs are occasionally added to large-volume parenterals prior to, or during procedures, including surgery. The FDA has recently updated CPG 635.100, Large Volume Parenterals (LVP) for Animal Use, indicating that LVP may be considered new animal drugs. In the absence of FDA approval of these LVP, they are unapproved new animal drugs, presumably falling outside the scope of compounding under the Animal Medicinal Drug Use Clarification Act (AMDUCA) and 21 CFR Part 530, but draft GFI # 256 does not explicitly indicate whether they are, or are not, within the scope of compounding from bulk drug substances.

Establishment registration and drug listing
Veterinary clinics frequently repackage drugs that are FDA-approved for use in humans and other animals for the convenience of their clients. FDA CPG 625.500 seems to indicate that veterinary clinics engaged in the manufacture, preparation, propagation, compounding or processing of veterinary drugs are subject to registration and drug listing under Section 510 of the Federal Food, Drug, and Cosmetic Act, and are not exempt under any of the provisions of 21 CFR Part 207. The sample warning letter language refers to repackaging. Accordingly, we would appreciate clarity around requirements for establishment registration and drug listing.

Request for extension of the comment period
Given uncertainties in the status of USP <795> and <797>, we request clarity of intent, followed by additional time to gather and compile input from veterinarians regarding the applicability of USP chapters to licensed veterinarians (who are not compounding drugs for resale) to complete our comment submission.

In addition, veterinarians would appreciate clarity, and subsequently more time to comment, on whether FDA intends to take enforcement action against compounding from bulk drug substances in the case of:

- drugs listed in, and used in accordance with, AVMA's euthanasia or depopulation guidelines that need to be compounded because the FDA-approved drug(s) are not available, or not feasible to use in a particular situation. This assumes such compounded drugs are in compliance with CPGs 608.300 and 650.100 whether used in food-producing or non-food-producing animals.
- drugs used for immobilization or animal capture that need to be compounded because FDA-approved drugs are not available or not feasible to use in a particular situation (possibly if on an AVMA or FDA list), whether intended to be used in non-food-producing animals or food-producing

minor species. Again, this assumes such compounded drugs are used in compliance with CPG 608.300.

- large volume parenterals used in non-human animals in compliance with CPG 635.100, including the addition of FDA-approved sterile injectable drugs to large volume parenterals when administered to the patient by or under the direct supervision of the licensed veterinarian within 4 hours.

The AVMA and its member veterinarians would also appreciate clarity around whether FDA intends to take enforcement action against veterinarians who do not register their veterinary clinic or drug list compounded drugs, if they compound drugs that are FDA-approved for use in humans or other animals, in their private practice for use by their clients, but not for resale. Again, once FDA clarifies its intent, we would appreciate additional time to react to that additional information.

The AVMA, founded in 1863, is one of the oldest and largest veterinary medical organizations in the world, with more than 95,000 member veterinarians worldwide engaged in a wide variety of professional activities and dedicated to the art and science of veterinary medicine. We thank the FDA for considering our request to extend the comment period. For questions regarding the AVMA's request, please contact Dr. Dharati Szymanski at 847-285-6742 or dszymanski@avma.org or Dr. Ashley Morgan at 202-289-3210 or amorgan@avma.org.

Sincerely,

Janet D. Donlin, DVM, CAE
Executive Vice President and Chief Executive Officer

DS/MM/AM/GCG