Updated August 25, 2020

DRAFT Feedback on FDA's draft GFI #256
Compounding Animal Drugs from Bulk Drug Substances

The **AVMA supports**

- Three general sets of circumstances in which compounding from bulk drug substances may be medically necessary:
  - The approved product is not commercially available,
  - The needed compounded preparation cannot be made from the approved product, or
  - There is no approved product from which to compound the needed preparation.
- Requirement that a veterinarian-client-patient relationship as defined by FDA must exist for use of a compounded preparation in an animal patient.
- For food-producing animals, a publicly available, current list of unapproved bulk drug substances that can be used to compound when a veterinarian-client-patient relationship exists and that is specific and limited to products used for euthanasia, depopulation, and as poison antidotes. AVMA asserts that if adequate scientific information is not available to determine a withdrawal time, the compound cannot and should not be used in a food animal or the treated animal cannot enter the food supply.
- The veterinarian's ability to maintain sufficient quantities of compounded preparations in their office for urgent administration or dispensing in emergency situations.
- Requirement that compounding occur under the direct supervision of the veterinarian or pharmacist and that, in the case of a pharmacist, such compounding occur in a state-licensed pharmacy or federal facility. (III.A.1.; III.B.1.; III.C.1)
- Provisions that address concerns regarding compounded preparations that:
  - Pose safety risks for animals to be treated and for people handling or administering the medication.
  - Are intended for use in food-producing animals because of the risk of drug residues in the meat, milk, or eggs consumed by people.
  - Are copies of FDA-approved, conditionally approved, or indexed drugs. Copies undermine incentives for sponsors to pursue drug approval. The AVMA supports the FDA's drug approval process because we want products that have been demonstrated to be safe, effective, properly manufactured following cGMP requirements, accurately labelled, and subject to post-approval requirements.
  - Are sold as office stock. Preparations compounded without a patient-specific prescription (office stock) can potentially expose large numbers of animals to drugs of unproven safety, quality, and effectiveness.
- With conditions, requirements that the drug be 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 in compliance 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). The AVMA notes there are provisions within USP's chapters that are not always relevant, appropriate, or applicable to veterinarians or pharmacists compounding medications for animal patients. The AVMA is working closely with the USP to create a veterinary-specific compounding

chapter. **We ask that FDA update GFI # 256, or any successors, at such time as other relevant USP chapters become available.** (III.A.2.; III.B.3.).

- Requiring that the compounded drug be dispensed:
  - Directly from the pharmacist to the veterinarian or to the patient's owner or caretaker,
  - By the veterinarian to the owner or caretaker of their animal patient, or
  - To another veterinarian in the same practice located in the same physical location.

  We likewise agree that the compounded drug should not be otherwise dispensed or transferred by the pharmacy, pharmacist, or veterinarian to a third party (e.g., distributor, retailer, or a veterinarian in another practice). (III.A.3.; III.B.4.)
- Proper labeling of all dispensed prescription medications, including requirements set forth in this guidance. (III.A.8.; III.B.6.; III.C.5.) See additional comments related to refinement of adverse event reporting below.

The **AVMA seeks further collaboration on**

- Developing and strengthening the adverse event reporting system. **We ask that FDA engage in dialogue with veterinarians and pharmacists about the appropriate system and method to be used for reporting adverse events associated with compounded products as we have concerns about the proposed use of Form FDA 1932a**. (III.A.7; III.A.8.; III.B.5.; III.B.6; III.C.4.; III.C.5.)

AVMA Feedback on Specific Sections

Section III. A.

- (4) and (5): The AVMA believes that a compounded animal drug should not be a copy of an FDA-approved, conditionally approved, or indexed product.

  We ask that FDA strike references to "clinical difference" as they appear in III.A.4 and III.A.5. As shared in our feedback on previous draft guidance on compounding for animals from bulk drug substances (draft GFI #230), the AVMA contends that a medical rationale documented in the patient's record is what is necessary for creation and use of a compounded preparation. We believe the phrase "clinical difference" does not capture other considerations that might create a need for a compounded preparation, such as certain worker and client safety needs, client compliance, and the potential for creating unnecessary animal stress (e.g., cats that cannot be safely and compliantly pilled). These needs are not related to "clinical differences," per se, but rather, the ability to successfully and safely medicate patients.

  We agree that documentation of why the compounded preparation was chosen is appropriate for the medical record; however, the AVMA disagrees with the requirement that a veterinarian include the medical rationale on the prescription for the product. **We also request that FDA strike language in III.A.4. and III.A.5. requiring the veterinarian to document the medical rationale on the prescription**.

- (4)(c): The **AVMA requests clarification** regarding the definition of a copy in having the same, similar, or easily substitutable strength as an approved product where a same or similar dosage can be achieved by administration of fractional or multiple doses of a drug product. There are no parameters describing what would be considered a reasonable fractional dose or a reasonable number of multiple doses that would be required to achieve the desirable dosage.

- (6): The **AVMA supports** requirements that the entity compounding the drug determine and document the reason(s) why an FDA-approved, conditionally approved, or indexed animal drug(s) or an FDA-approved human drug(s) cannot be used as the source of the active ingredient(s).

Section III. B.

- (2): **As proposed, AVMA opposes the use of a list to determine the appropriateness of compounding from bulk drug substances for office stock drugs for use in nonfood-producing animals**. Veterinary medicine is unique in that we treat a multitude of nonfood-producing species with unique diseases and conditions, many of which need to be treated expediently. We believe the level of detail FDA is requiring (see Appendix: 4. Information Requested for FDA to Evaluate Nominated Bulk Drug Substances for Inclusion on the List, [b]-[h]) to accompany all nominations will restrict the number of bulk drug substances available for use in office stock and prevent veterinarians from meeting the urgent and emergent needs of our patients, which may result in animal suffering and, potentially, death.

  We do not believe creating a "positive" list, as currently conceived, is practicable because:
  - The supporting information that FDA requires to consider adding a substance to the list will be next to impossible to provide for all of the bulk drug substances needed to prepare office stock to treat urgent needs of nonfood-producing animals;
  - There are no provisions proposed to address needs during times of shortage; and
  - There are no provisions to provide for special consideration for bulk drug substances needed to prepare drugs for nonfood minor species and bulk drug substances that are not found as active ingredients in FDA-approved, conditionally approved, or indexed drugs.

  We request that FDA amend provision III.B.2. to strike the reference to a list and insert language from the Appendix to read as follows:

  Section III.B.
  2. The drug is intended for use in a nonfood-producing species and is compounded from a bulk drug substance ~~listed on FDA's "List of Bulk Drug Substances for Compounding Office Stock Drugs for Use in Nonfood-Producing Animals or Antidotes for Food-Producing Animals" (https://www.fda.gov/animal-veterinary/animal-drug-compounding/list-bulk-drug-substances-compounding-office-stock-drugs-use-nonfood-producing-animals-or-antidotes) described in the appendix to this guidance;~~ when—

  i. There is no commercially available ~~marketed~~ FDA-approved, conditionally approved, or indexed animal drug that can be used as labeled to treat the condition;
  ii. There is no commercially available ~~marketed~~ FDA-approved animal or human drug that could be used in an extralabel manner under section 512(a)(4) or (a)(5) of the FD&C Act and 21 CFR part 530 to treat the condition;
  iii. The drug cannot be compounded from a commercially available ~~marketed~~ FDA-approved animal or human drug consistent with 21 CFR part 530;
  iv. Immediate treatment with the compounded drug is necessary to avoid animal suffering or death; and

v. FDA has not identified a significant safety concern specific to use of the bulk drug substance in animals.

Section III.C.

- (2): The **AVMA supports** a list of bulk drug substances for compounding office stock drugs for poison antidotes for food-producing animals, so long as bulk drug substances used to compound drugs used for depopulation and euthanasia are also included on that list (see policy).
- (3): **We request FDA amend** this provision as follows: "The veterinarian ~~establishes~~ specifies and documents a scientifically based withdrawal time that ensures residues of the antidote and the underlying toxin are not present in the animal at the time of slaughter or the veterinarian ensures the animal does not enter the food supply."
- **AVMA requests** that the active ingredients for those drugs in the AVMA's euthanasia and depopulation guidelines for which an FDA-approved, conditionally approved, or indexed drug is not available be added or incorporated by reference into the list for use in food-producing animals.