Informational Summary of
New DRAFT FDA Guidance for Industry #256, "Compounding Animal Drugs from Bulk Substances"

AVMA members are encouraged to submit feedback to compounding@avma.org by January 17, 2020

The U.S. Food and Drug Administration (FDA) has released new draft Guidance for Industry (GFI), titled #256 "Compounding Animal Drugs from Bulk Substances." In May 2015, the FDA CVM introduced draft guidance for animal drug compounding that did not meet the needs of veterinarians. Following significant feedback from the AVMA, other veterinary organizations, and individual veterinarians, the agency formally withdrew that guidance in November 2017. The FDA intends for its new guidance to balance its concerns regarding safety, effectiveness, and quality of animal drugs compounded from bulk substances with the desire to provide treatment options for the diversity of veterinary species with their myriad of disease conditions. The FDA states that because of the safety benefits and protections derived from pre-market review and post-market monitoring of FDA-approved, conditionally approved, and indexed drugs, a veterinarian should only use drugs compounded from bulk drug substances if FDA-approved, conditionally approved, or indexed drugs are not available to treat their patient.

While the Agency maintains that compounding of a new animal drug from bulk drug substances results in a new animal drug that must comply with the federal Food Drug and Cosmetic Act's approval, conditional approval, or indexing requirements, the FDA does not intend to take enforcement action for violations when the following conditions are met:

- compounding is performed by or under the direct supervision of a veterinarian or pharmacist;
- the product is dispensed by a pharmacist after receiving a prescription from a veterinarian who has an established veterinarian-client-patient relationship or dispensed directly by the veterinarian;
- compounding occurs according to USP <795> "Pharmaceutical Compounding — Nonsterile Preparations" and USP <797> "Pharmaceutical Compounding — Sterile Preparations" and complies with the standards of all applicable USP-NF monographs;
- the pharmacist or veterinarian reports an adverse event or drug defect to the FDA within 15 days;
- labelling requirements as outlined in the GFI are met.

However, the FDA has indicated that additional requirements apply depending on whether the product is intended as a patient-specific product in a non-food-producing animal, as office stock for non-food-producing animals, or as an antidote for food-producing animals.

For patient-specific prescriptions for non-food-producing animals:

- the compounded drug cannot be a copy of a marketed FDA-approved, conditionally approved, or indexed animal drug or FDA-approved human drug. A copy contains the same active pharmaceutical ingredient, can be given by the same route of administration, and is of the same, similar, or a substitutable strength. The FDA will not consider a compounded product a copy if the prescribing veterinarian determines there is a difference between the compounded

drug and the approved/indexed drug that will produce a clinical difference in the identified patient and the medical rationale is documented.

- if the compounded drug has the same active pharmaceutical ingredient as an FDA-approved, conditionally approved, or indexed drug or an FDA-approved human drug, but is a different salt, ester, or other noncovalent derivative (e.g., erythromycin stearate as compared with erythromycin ethyl succinate), then the compounded product must produce a clinical difference, and the medical rationale for such use must be documented on the prescription, if dispensed by the pharmacist, or on the medical record, if dispensed by the veterinarian.
- if the compounded drug has the same active pharmaceutical ingredient as one or more marketed FDA-approved, conditionally approved, or indexed drugs or an FDA-approved human drug, then the compounder must determine and document why the approved product cannot be used to prepare the compound before using a bulk drug substance as the source of the active ingredient.

For office stock (compounding without patient-specific prescriptions) for non-food-producing animals:

- the bulk drug substance must be on the FDA's "List of Bulk Drug Substances for Compounding Office Stock Drugs for Use in Non-Food-Producing Animals or Antidotes for Food-Producing Animals";
- the drug cannot be transferred or dispensed to a third party, such as a retailer or another veterinarian at a different location.

For antidotes for food-producing animals:

- the bulk drug substance must be 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";
- the veterinarian must document 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 ensure the animal does not enter the food supply.

The FDA is seeking comments on draft GFI #256 and has requested submission of those comments by February 18, 2020. We encourage members to submit their feedback to AVMA at compounding @avma.org by January 17, 2020.

In addition, the FDA is requesting nominations to the list of bulk drug substances for compounding: "List of Bulk Drug Substances for Compounding Office Stock Drugs for Use in Non-Food-Producing Animals or Antidotes for Food-Producing Animals". Those interested in submitting nominations need to refer to and include the information requested by the FDA for each drug nomination.

The FDA has posted two related lists:

- "Nominated Bulk Drug Substances That May Not Be Used to Compound Office Stock Drugs or Antidotes for use in Food-Producing Animals"
- "Bulk Drug Substances Nominated without Sufficient Support"

The AVMA will submit a collated response to the FDA as we continue our efforts to advocate for access to needed medications on behalf of the profession.