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New Draft Guidance on Veterinary Drug Compounding from Bulk Drug Substances

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Food, Drugs, and Devices

Last week, the United States Food and Drug Administration (FDA) Center for Veterinary Medicine (CVM) published Draft Guidance for Industry No. 256, "Compounding Animal Drugs from Bulk Drug Substances" (Draft Guidance).[1] FDA had issued a draft guidance on this topic in May 2015,[2] but the Agency withdrew that guidance without finalizing it.[3] The new Draft Guidance describes circumstances under which CVM intends to exercise enforcement discretion with regard to animal drug compounding from bulk drug substances (compounding from bulk). The comment period ends on **February 18, 2020**.

Background

The Federal Food, Drug, and Cosmetic Act (FDCA) does not address compounding animal drugs from bulk. The FDCA section 503A and 503B exemptions applicable to compounded human drugs do not apply to animal drugs. Drug compounding for animals is regulated under the Animal Medicinal Drug Use Clarification Act of 1994 (AMDUCA), which also regulates extra-label drug use in animals. Section 530.13 of 21 C.F.R. specifies the conditions under which CVM permits drug compounding for animals using modified approved animal or human drugs under specific circumstances: "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 C.F.R. § 530.13(a).

Although the FDCA and its implementing regulations do not authorize compounding animal drugs from bulk, CVM has recognized the need for such drugs in limited circumstances. The Draft Guidance therefore elucidates an enforcement discretion policy for veterinary drugs compounded from bulk provided the compounder meets certain conditions. The policy requires that the veterinarian act within a valid veterinarian-client-patient relationship (VPCR), and that

[1] 84 Fed. Reg. 64,085 (Nov. 20, 2019).

[2] 80 Fed. Reg. 28624 (May 19, 2015).

[3] "FDA Announces Withdrawal of Draft Guidance for Industry #230 Regarding Animal Drug Compounding," https://www.fda.gov/animal-veterinary/cvm-updates/fda-announces-withdrawal-draft-guidance-industry-230-regarding-animal-drug-compounding.

there be no medically appropriate approved, conditionally approved or indexed drug in the particular case.

The Draft Guidance also recognizes that despite the desirability of limiting "office stock" compounded from bulk, *i.e.*, non-patient specific compounded drugs a veterinarian keeps on hand, having such drugs available when a patient that needs them presents can sometimes prevent animal suffering or death. CVM proposes to limit office stock compounded from bulk to those drug products appearing on a list, as discussed below.

Draft Guidance

The Draft Guidance describes conditions under which CVM intends to exercise enforcement discretion for violations of FDCA sections 512 and 501(a)(5) (new drug approval), 502(f)(1) (labeling with adequate directions for use), and 501(a)(2)(B) (current good manufacturing practice) when compounders produce animal drugs from bulk. These include:

- The compounding is by or under the direct supervision of a veterinarian or a pharmacist in a State-licensed pharmacy or Federal facility;
- It meets standards in current United States Pharmacopeia Chapters <795> (non-sterile compounded preparations) or <797> (compounded sterile preparations);
- The drug is not a copy of a marketed FDA-approved, conditionally approved, or indexed animal drug or an FDA-approved human drug;
- If the compounded drug contains the same active moiety as a marketed animal drug or human drug but as a different salt, ester, or other noncovalent derivative, the compounder documents a clinical difference between the drugs or why the marketed animal drug or human drug cannot be used;
- The compounder meets adverse event reporting and product defect reporting obligations;
- The compounder labels the compounded drug with certain information; and
- The compounder adheres to certain restrictions on third-party transfers.

Additional conditions vary based on whether the compounder produces the compounded drug for a specific patient, for office stock, or, in food-producing animals, for use as antidote.

CVM is developing and intends to apply its enforcement discretion policy to the entries on a list of drugs compounded from bulk and intended as office stock, and is actively seeking nominations for such entries. Criteria for the list include:

- There is no FDA-approved, conditionally approved, or indexed animal drug that can be used as labeled to treat the condition;
- There is no marketed FDA-approved animal or human drug that can be used in an extralabel manner to treat the condition in accordance with the FDCA and its regulations;
- The drug cannot be compounded from a marketed FDA-approved animal or human drug;
- Immediate treatment is necessary to avoid animal suffering or death;

- FDA has not identified a significant safety concern with the drug compounded from bulk; and
- For drugs for use as antidotes in food-producing animals, there is sufficient scientific information for the veterinarian to determine appropriate withdrawal, withholding, or discard times for food which might be derived from the treated animal.

For food-producing animals, the veterinarian also either establishes and documents a withdrawal time to ensure that the animal is free of any residues at the time of slaughter, or prevents the animal from entering the food supply.

Considerations for Comments

In drafting comments, companies may want to consider whether the conditions aimed at preventing compounders from undermining the drug approval process are sufficiently robust. For example, it appears that those conditions can be satisfied by a compounder unilaterally--without consulting a veterinarian--determining and documenting that its compounded drug does not constitute a "copy" of an approved drug as that term is defined in the Draft Guidance.

Companies may also want to consider whether restricting office stock compounding to bulk drug substances that appear on a list will prevent large-scale, nationwide distribution that undermines the incentives for manufacturers to seek FDA approval of those drugs.

Finally, FDA specifically invites comment on the subject of section III.A.5 of the Draft Guidance, which provides

> that if a compounded drug contains the same active moiety as a marketed FDA-approved, conditionally approved, or indexed animal drug or an FDA-approved human drug but as a different salt, ester, or other noncovalent derivative, there should be a difference between the compounded drug and the FDA-approved, conditionally approved, or indexed animal drug or FDA-approved human drug that will produce a clinical difference in the patient and the medical rationale is documented in the prescription, or if a veterinarian is compounding the drug, the medical rationale is noted in the patient's medical record.[4]

The Draft Guidance notes CVM's concern that using a different salt, ester, or other noncovalent derivative of the same active moiety can affect the quality (*e.g.*, stability) of the drug and its overall safety and effectiveness as well as that such compounding could undermine incentives for new drug research and development.

[4] 84 Fed. Reg. 64,085.

If you have any questions concerning the material discussed in this client alert, please contact the following members of our Food & Drug practice group.

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