

To: Board Members

Subject: AGENDA ITEM VI Consideration of Comments on the FDA's Draft Guidance Document #230 On Compounding Animal Drugs from Bulk Substances

This matter was discussed by the Enforcement Committee at its September 9, meeting, and was subsequently made an action item for the next board meeting.

The Board of Pharmacy previously expressed interest in submitting comments on the FDA's Guidance Document 230, "Compounding Animal Drugs from Bulk Substances."

The following provides an overview and summary of the guidance provided in the FDA's guidance document. The guidance document is provided in **Attachment I** following this memo.

The guidance supports and reinforces the regulatory framework developed by FDA for pharmacies and outsourcers who compound human drugs with several exceptions.

- For pharmacies that compound medications for animal use, the FDA guidance states that a veterinarian's prescription is required for the specific animal. The prescription must contain the standard information required on all prescriptions but also must include:
 1. The name and species of the animal
 2. A statement that the animal is not a food-producing animal
 3. If a manufactured drug exists, a statement that the compounded product would make a clinical difference from the manufactured product

The guidance provides that pharmacies that compound such drugs must do so pursuant to USP 795 and 797 standards, by or under the supervision of a pharmacist, and such compounded products may not be distributed by wholesalers.

Finally, the guidance allows a pharmacy to compound for future furnishing but is limited to the maximum quantity of that drug dispensed in a 14-day period within the last six months.

- For outsourcing facilities that compound animal drugs from bulk substances, the FDA is developing a list (which is not yet completed) of approved drug substances that an outsourcing facility must use when compounding for animals, linked to the species and the condition.

The compounding must be done in accordance with cGMP standards by or under the supervision of a pharmacist. Outsourcing facility-compounded drugs may not be used on or in food producing animals, and must be expressly labeled to state this prohibition.

The veterinarian must note on the order or prescription that the veterinary drug is intended to treat a specific condition and specific species, and this must match the listing on the FDA's bulk drug substances list. The guidance specifies labeling requirements and a statement on the label that the product is not for resale. The guidance also requires that any drugs compounded by an outsourcing facility must be reported on the biannual lists of products compounded that must be sent to the FDA, with a notation of the products intended for animals.

- The guidance also permits compounding by a veterinarian.

Committee Recommendation

After discussion at the September 9th meeting, the Enforcement Committee made the following recommendation: Submit comments to the FDA in support of the policy articulated in the FDA Compounding Animal Drugs from Bulk Substances Guidance Document.

Attachment 1

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#230

Guidance for Industry Compounding Animal Drugs from Bulk Drug Substances

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to <http://www.regulations.gov>. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact Eric Nelson (CVM) at 240-402-5642, or by e-mail at eric.nelson@fda.hhs.gov.

**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Veterinary Medicine (CVM)**

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Guidance for Industry¹ **Compounding Animal Drugs from Bulk Drug Substances**

This draft guidance, when finalized, represents the Food and Drug Administration's (FDA or Agency) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this draft guidance using the contact information on the title page of this guidance.

I. INTRODUCTION AND SCOPE

This draft guidance sets forth the Food and Drug Administration's ("FDA") policy regarding compounding animal drugs from bulk drug substances² by state-licensed pharmacies, licensed veterinarians, and facilities that register with FDA as outsourcing facilities under section 503B of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 353b). This guidance reflects FDA's current thinking regarding compounding animal drugs from bulk drug substances and describes the conditions under which FDA generally does not intend to take action for violations of the following sections of the FD&C Act: section 512 (21 U.S.C. 360b), section 501(a)(5) (21 U.S.C. 351(a)(5)), section 502(f)(1) (21 U.S.C. 352 (f)(1)), and, where specified, section 501(a)(2)(B) (21 U.S.C. 351(a)(2)(B)), when a state-licensed pharmacy, licensed veterinarian, or an outsourcing facility³ compounds animal drugs from bulk drug substances.

This draft guidance only addresses the compounding of animal drugs from bulk drug substances. It does not apply to the compounding of animal drugs from approved new animal or new human drugs. Such compounding can be conducted in accordance with the provisions of section 512(a)(4) and (5) of the FD&C Act (21 U.S.C. 360b(a)(4) and (5)) and 21 CFR part 530. In addition, this draft guidance does not address the compounding of drugs intended for use in

¹ This draft guidance has been prepared by the Center for Veterinary Medicine (CVM) in consultation with the Center for Drug Evaluation and Research (CDER) and the Office of Regulatory Affairs (ORA) at the Food and Drug Administration.

² FDA regulations define "bulk drug substance" as "any substance that is represented for use in a drug and that, when used in the manufacturing, processing, or packaging of a drug, becomes an active ingredient or a finished dosage form of the drug, but the term does not include intermediates used in the synthesis of such substances." 21 CFR 207.3(a)(4). "Active ingredient" is defined as "any component that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body of man or other animals. The term includes those components that may undergo chemical change in the manufacture of the drug product and be present in the drug product in a modified form intended to furnish the specified activity or effect." 21 CFR 210.3(b)(7). Any component other than an active ingredient is an "inactive ingredient." See 21 CFR 210.3(b)(8). Inactive ingredients used in compounded drug products commonly include flavorings, dyes, diluents, or other excipients.

³ "Outsourcing facility" refers to a facility that meets the definition of an outsourcing facility under section 503B(d)(4) of the FD&C Act. See draft guidance for industry *For Entities Considering Whether to Register As Outsourcing Facilities Under Section 503B of the Federal Food, Drug, and Cosmetic Act*.

<http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm434171.pdf>.

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humans, which is addressed in other guidances.⁴ Further, the draft guidance does not address new animal drugs for investigational use. See 21 CFR part 511.

FDA's guidance documents, including this draft guidance, do not establish legally enforceable responsibilities. Instead, guidances describe FDA's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in FDA guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

A. Regulatory Framework

To be legally marketed, new animal drugs must be approved under section 512 of the FD&C Act, conditionally approved under section 571 of the FD&C Act (21 U.S.C. 360ccc), or included on the Index of Legally Marketed Unapproved New Animal Drugs for Minor Species under section 572 of the FD&C Act (21 U.S.C. 360ccc-1). The FD&C Act does not generally distinguish between compounding and other methods of animal drug manufacturing. Animal drugs that are not approved or indexed are considered "unsafe" under section 512(a)(1) of the FD&C and adulterated under section 501(a)(5) of the FD&C Act.

Although sections 503A (21 U.S.C. 353a) and 503B of the FD&C Act provide certain statutory exemptions for compounded human drugs, these sections do not provide exemptions for drugs compounded for animal use. The compounding of an animal drug from bulk drug substances results in a new animal drug that must comply with the FD&C Act's approval/indexing requirements.⁵ Further, all animal drugs are required to, among other things, be made in accordance with current good manufacturing practice (cGMP) requirements (section 501(a)(2)(B)) of the FD&C Act and 21 CFR parts 210 and 211) and have adequate directions for use (section 502(f)(1) of the FD&C Act).

Sections 512(a)(4) and (5) of the FD&C Act provide a limited exemption from certain requirements for compounded animal drugs made from already approved animal or human drugs. Such use is considered an extralabel use and the FD&C Act provides an exemption from the approval requirements and requirements of section 502(f) of the FD&C Act for extralabel uses that meet the conditions set out in the statute and FDA regulations at 21 CFR part 530. Among other things, these regulations specify that nothing in the regulations should be construed as permitting compounding animal drugs from bulk drug substances.

In 1996, FDA announced the availability of a CPG (section 608.400) entitled, "Compounding of Drugs for Use in Animals" (61 FR 34849, July 3, 1996), to provide guidance to FDA's field and headquarters staff with regard to the compounding of animal drugs by veterinarians and pharmacists. An updated CPG was made available on July 14, 2003 (68 FR 41591). This draft guidance supersedes that CPG, which has now been withdrawn.

⁴ <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm166743.htm>.

⁵ See *Medical Center Pharmacy v. Mukasey*, 536 F.3d 383, 394 (5th Cir. 2008).

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B. Compounding Animal Drugs

Numerous drugs are approved or indexed for use in animals. However, there are many different species of animals with different diseases and conditions for which there are no approved or indexed animal drugs. In some cases, approved human drugs can be used to treat an animal under the extralabel use provisions of the FD&C Act and FDA regulations (sections 512(a)(4) and (a)(5) of FD&C Act and 21 CFR part 530). For example, various chemotherapeutic drugs approved for humans are used to treat cancer in dogs and cats. FDA recognizes that there are circumstances where there is no drug available to treat a particular animal with a particular condition, because either no drug is approved for a specific animal species or no drug is available under the extralabel drug use provisions. In those limited circumstances, an animal drug compounded from bulk drug substances may be an appropriate treatment option.

However, FDA is concerned about the use of animal drugs compounded from bulk drug substances, especially when approved alternatives exist that can be used as labeled or in an extralabel manner consistent with the requirements of FDA's extralabel provisions. Compounded drugs have not undergone premarket FDA review of safety, effectiveness, or manufacturing quality. The unrestricted compounding of animal drugs from bulk drug substances has the potential to compromise food safety, place animals or humans at undue risk from unsafe or ineffective treatment, and undermine the incentives to develop and submit new animal drug applications to FDA containing data and information to demonstrate that the product is safe, effective, properly manufactured, and accurately labeled.

III. POLICY

As discussed above, animal drugs are generally subject to the adulteration, misbranding, and approval provisions of the FD&C Act. Generally, FDA does not intend to take action under sections 512(a), 501(a)(5), 502(f)(1) and 501(a)(2)(B) of the FD&C Act if a state-licensed pharmacy or a licensed veterinarian compounds animal drugs from bulk drug substances in accordance with the conditions described below, and the drug is not otherwise adulterated or misbranded. In addition, FDA generally does not intend to take action under sections 512(a), 501(a)(5), and 502(f)(1) of the FD&C Act if an outsourcing facility compounds animal drugs in accordance with all of the applicable conditions described below, and the drug is not otherwise adulterated or misbranded.

FDA's decision not to take enforcement action depends on its ability to evaluate whether the compounding of animal drugs is in accordance with the conditions below. Therefore, entities compounding animal drugs should keep adequate records to demonstrate that they are compounding such drugs in accordance with all of the applicable conditions described below.

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The conditions referred to above are as follows:

- A. If the animal drug is compounded in a state-licensed pharmacy:
1. The drug is compounded by or under the direct supervision of a licensed pharmacist.
 2. The drug is dispensed after the receipt of a valid prescription from a veterinarian for an individually identified animal patient that comes directly from the prescribing veterinarian or from the patient's owner or caretaker to the compounding pharmacy. A drug may be compounded in advance of receipt of a prescription in a quantity that does not exceed the amount of drug product that the state-licensed pharmacy compounded pursuant to patient-specific prescriptions based on a history of receipt of such patient-specific prescriptions for that drug product over any consecutive 14-day period within the previous 6 months.
 3. The drug is not intended for use in food-producing animals, and the prescription or documentation accompanying the prescription for the drug contains the statement "This patient is not a food-producing animal." For purposes of this draft guidance, all cattle, swine, chicken, turkey, sheep, goats, and non-ornamental fish are always considered to be food-producing animals regardless of whether the specific animal or food from the specific animal is intended to be introduced into the human or animal food chain (e.g., pet pot-bellied pigs and pet chicks are always considered to be food-producing animals). In addition, for purposes of this draft guidance, any other animal designated on the prescription or in documentation accompanying the prescription by the veterinarian as a food-producing animal, regardless of species, is considered to be a food-producing animal (e.g., rabbits, captive elk, captive deer).
 4. If the drug contains a bulk drug substance that is a component of any marketed FDA-approved animal or human drug:
 - a. there is a change between the compounded drug and the comparable FDA-approved animal or human drug made for an individually identified animal patient that produces a clinical difference for that individually identified animal patient, as determined by the veterinarian prescribing the compounded drug for his/her patient under his/her care, and
 - b. the prescription or documentation accompanying the prescription contains a statement that the change between the compounded drug and the FDA-approved drug would produce a clinical difference for the individually identified animal patient. For example, the veterinarian could state that, "Compounded drug X would produce a clinical difference for the individually identified animal patient because the approved drug is too large a dose for the animal and cannot be divided or diluted into the small dose required."
 5. If there is an FDA-approved animal or human drug with the same active ingredient(s), the pharmacy determines that the compounded drug cannot be made from the FDA-approved drug(s), and documents that determination.

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6. The pharmacy receives from the veterinarian (either directly or through the patient's owner or caretaker), in addition to any other information required by state law, the following information, which can be documented on the prescription or documentation accompanying the prescription:
 - a. Identification of the species of animal for which the drug is prescribed; and,
 - b. The statement "There are no FDA-approved animal or human drugs that can be used as labeled or in an extralabel manner under section 512(a)(4) or (5) and 21 CFR part 530 to appropriately treat the disease, symptom, or condition for which this drug is being prescribed."
 7. Any bulk drug substance used to compound the drug is manufactured by an establishment that is registered under section 510 of the FD&C Act (21 U.S.C. 360) (including a foreign establishment that is registered under section 510) and is accompanied by a valid certificate of analysis.
 8. The drug is compounded in accordance with Chapters <795> and <797> of the United States Pharmacopeia and National Formulary (USP—NF)⁶ (e.g., a sterile drug is compounded in an area with air quality that meets or exceeds ISO Class 5 standards (see USP—NF Chapter <797>, Table 1)).
 9. The drug is not sold or transferred by an entity other than the entity that compounded such drug. For purposes of this condition, a sale or transfer does not include administration of a compounded drug by a veterinarian to a patient under his or her care.
 10. Within 15 days of becoming aware of any product defect or serious adverse event associated with animal drugs it compounded from bulk drug substances, the pharmacy reports it to FDA on Form FDA 1932a. Form FDA 1932a can be downloaded at <http://www.fda.gov/downloads/aboutfda/reportsmanualsforms/forms/animaldrugforms/ucm048817.pdf>.
 11. The label of any compounded drug indicates the species of the intended animal patient, the name of the animal patient and the name of the owner or caretaker of the animal patient.
- B. If the animal drug is compounded by a licensed veterinarian:
1. The drug is compounded and dispensed by the veterinarian to treat an individually identified animal patient under his or her care.

⁶ Chapters <795> *Pharmaceutical Compounding—Nonsterile Preparations* and <797> *Pharmaceutical Compounding—Sterile Preparations* can be found in the combined *United States Pharmacopeia and National Formulary (USP-NF)*, available at <http://www.usp.org>.

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2. The drug is not intended for use in food-producing animals as defined in section III.A.3 of this guidance.
 3. If the drug contains a bulk drug substance that is a component of any marketed FDA-approved animal or human drug, there is a change between the compounded drug and the comparable FDA-approved animal or human drug made for an individually identified animal patient that produces a clinical difference for that individually identified animal patient, as determined by the veterinarian prescribing the compounded drug for his/her patient under his/her care.
 4. There are no FDA-approved animal or human drugs that can be used as labeled or in an extralabel manner under sections 512(a)(4) and (5) of the FD&C Act and 21 CFR part 530 to appropriately treat the disease, symptom, or condition for which the drug is being prescribed.
 5. The drug is compounded in accordance with USP—NF Chapters <795> and <797> (e.g., a sterile drug is compounded in an area with air quality that meets or exceeds ISO Class 5 standards (see USP—NF Chapter <797>, Table 1)).
 6. Any bulk drug substance used is manufactured by an establishment that is registered under section 510 of the FD&C Act (21 U.S.C. 360) (including a foreign establishment that is registered under section 360(i)) and is accompanied by a valid certificate of analysis.
 7. The drug is not sold or transferred by the veterinarian compounding the drug. For purposes of this condition, a sale or transfer does not include administration of a compounded drug by the veterinarian to a patient under his or her care, or the dispensing of an animal drug compounded by the veterinarian to the owner or caretaker of an animal under his or her care.
 8. Within 15 days of becoming aware of any product defect or serious adverse event associated with animal drugs the veterinarian compounded from bulk drug substances, he or she reports it to FDA on Form FDA 1932a. Form FDA 1932a can be downloaded at <http://www.fda.gov/downloads/aboutfda/reportsmanualsforms/forms/animaldrugforms/ucm048817.pdf>.
 9. The label of any compounded drug indicates the species of the intended animal patient, the name of the animal patient and the name of the owner or caretaker of the animal patient.
- C. If the animal drug is compounded by an outsourcing facility:
1. The drugs are compounded only from bulk drug substances appearing on Appendix A of this draft guidance.
 2. The drug is compounded by or under the direct supervision of a licensed pharmacist.

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3. The drug is not intended for use in food-producing animals, as defined in Section III.A.3 of this guidance, and the prescription or order, or documentation accompanying the prescription or order, for the drug contains the statement, “This drug will not be dispensed for or administered to food-producing animals.”
4. The drug is compounded in accordance with cGMP requirements.⁷
5. Any bulk drug substance used is manufactured by an establishment that is registered under section 510 of the FD&C Act (21 U.S.C. 360) (including a foreign establishment that is registered under section 360(i)) and is accompanied by a valid certificate of analysis.
6. The drug is not sold or transferred by an entity other than the outsourcing facility that compounded such drug. For purposes of this condition, a sale or transfer does not include administration of a compounded drug by a veterinarian to a patient under his or her care.
7. Within 15 days of becoming aware of any product defect or serious adverse event associated with animal drugs it compounded from bulk drug substances, the outsourcing facility reports it to FDA, on Form FDA1932a. Form FDA 1932a can be downloaded at <http://www.fda.gov/downloads/aboutfda/reportsmanualsforms/forms/animaldrugforms/ucm048817.pdf>.
8. All drugs compounded for animals by an outsourcing facility are included on the report required by section 503B of the FD&C Act to be submitted to the Food and Drug Administration each June and December identifying the drugs made by the outsourcing facility during the previous 6-month period, and providing the active ingredient(s); source of the active ingredient(s); NDC number of the source ingredient(s), if available; strength of the active ingredient(s) per unit; the dosage form and route of administration; the package description; the number of individual units produced; and the NDC number of the final product, if assigned.⁸ The outsourcing facility should identify which reported drugs were intended for animal use.
9. The veterinarian’s prescription or order states that the drug is intended to treat the species and condition(s) for which the substance is listed in Appendix A.

⁷ FDA intends to determine whether this condition is met by evaluating whether the facility complies with FDA regulations applicable to cGMPs for compounding of human drugs by outsourcing facilities. *See, e.g.*, draft guidance for industry, *Current Good Manufacturing Practice—Interim Guidance for Human Drug Compounding Outsourcing Facilities Under Section 503B of the FD&C Act* (July 2014), at

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM403496.pdf>

⁸ FDA has issued a draft guidance for industry, *Electronic Drug Product Reporting for Human Drug Compounding Outsourcing Facilities Under Section 503B of the Federal Food, Drug, and Cosmetic Act* (November 2014), which prescribes how human drug compounding facilities are to submit drug product reports to FDA. Available at <http://www.fda.gov/downloads/Drugs/NewsEvents/UCM424303.pdf>. Although this guidance addresses reporting of compounded human drug products, outsourcing facilities should follow the same procedure to electronically report the animal drug products they compounded.

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10. The label of the drug includes the following:
- a. Active ingredient(s).
 - b. Dosage form, strength, and flavoring, if any.
 - c. Directions for use, as provided by the veterinarian prescribing or ordering the drug.
 - d. Quantity or volume, whichever is appropriate.
 - e. The statement “Not for resale.”
 - f. The statement “For use only in [fill in species and any associated condition or limitation listed in Appendix A].”
 - g. The statement “Compounded by [name of outsourcing facility].”
 - h. Lot or batch number of drug.
 - i. Special storage and handling instructions.
 - j. Date the drug was compounded.
 - k. Beyond use date (BUD) of the drug.
 - l. Name of veterinarian prescribing or ordering the drug.
 - m. The address and phone number of the outsourcing facility that compounded the drug.
 - n. Inactive ingredients.
 - o. The statement “Adverse events associated with this compounded drug should be reported to FDA on a Form FDA 1932a.”
 - p. If the drug is compounded pursuant to a patient specific prescription, the species of the animal patient, name of the animal patient, and name of the owner or caretaker of the animal patient.

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APPENDIX A⁹

LIST OF BULK DRUG SUBSTANCES THAT MAY BE USED BY AN OUTSOURCING FACILITY TO COMPOUND DRUGS FOR USE IN ANIMALS

This Appendix, when finalized, will contain a list of bulk drug substances that may be used by facilities registered under section 503B as outsourcing facilities to compound animal drugs pursuant to a prescription from a veterinarian for an individually identified animal patient or pursuant to an order from a licensed veterinarian for veterinarian office use, and in accordance with any specified limitations or conditions.

This list will be developed with public input; the process for nominating bulk drug substances for this list is described in the Federal Register notice soliciting nominations for such bulk drug substances. FDA intends to limit the bulk drug substances in this Appendix to address situations where all of the following criteria are met:

- there is no marketed approved, conditionally approved, or index listed animal drug that can be used as labeled to treat the condition;
- there is no marketed approved animal or human drug that could be used under section 512(a)(4) or (a)(5) and 21 CFR Part 530 (addressing extralabel use of approved animal and human drugs) to treat the condition;
- the drug cannot be compounded from an approved animal or human drug;
- immediate treatment with the compounded drug is necessary to avoid animal suffering or death; and
- FDA has not identified a significant safety concern specific to the use of the bulk drug substance to compound animal drugs (under the listed conditions and limitations).

FDA intends to review the nominated bulk drug substances on a rolling basis and to periodically update this Appendix.

LIST:

⁹ To submit nominations for this list, refer to the Federal Register notice entitled, “List of Bulk Drug Substances That May be Used by an Outsourcing Facility to Compound Drugs for Use in Animals,” published May 19, 2015. After the period for nominations closes, you may petition FDA under 21 CFR 10.30 to add or remove specific listings.