#256B

Compounding Animal Drugs from Bulk Drug Substances: Compounding under CGMP in Federally-Registered Facilities

Draft Guidance

This guidance document is being distributed for comment purposes only.

This draft guidance, when finalized, will be combined with GFI #256, "Compounding Animal Drugs from Bulk Drug Substances."

Submit comments on this draft guidance by the dated provided in the *Federal Register* notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff, Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with docket number FDA-2018-D-4533.

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Additional copies of this draft guidance document may be requested from the Policy and Regulations Staff , Center for Veterinary Medicine, Food and Drug Administration, 5001 Campus Dr., College Park, MD 20740, and may be viewed on the Internet at https://www.fda.gov/animal-veterinary, https://www.fda.gov/regulatory-information/search-fda-guidance-documents, or http://www.regulations.gov.

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Compounding Animal Drugs from Bulk Drug Substances: Compounding under CGMP in Federally-Registered Facilities

Draft Guidance for Industry

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. Introduction

This draft guidance, when finalized, will describe the Food and Drug Administration's (FDA) enforcement policy regarding the compounding of animal drugs from bulk drug substances (also known as Active Pharmaceutical Ingredients (APIs))[1] when those drug products are compounded in accordance with current good manufacturing practice (CGMP)[2] in facilities registered with FDA under section 503B(b) or section 510(b) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (hereinafter "federally-registered facilities").[3]

This draft guidance does not cover animal drugs compounded for use in investigations of new animal drugs,[4] animal drugs compounded by a pharmacy that is not federally-registered, or animal drugs compounded from FDA-approved animal or human drugs.[5]

This draft guidance, when finalized, will be combined with GFI #256, "Compounding Animal Drugs from Bulk Drug Substances," which describes FDA's enforcement priorities for animal drugs compounded from bulk drug substances (BDS) by or under the direct supervision of

[1] FDA regulations define "bulk drug substance" and "active pharmaceutical ingredient" as "any substance that is intended for incorporation into a finished drug product and 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." The terms do not include intermediates used in the synthesis of the substance (21 CFR 207.1). "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" (21 CFR 210.3(b)(8)). Inactive ingredients used in compounded drug products commonly include flavorings, dyes, diluents, or other excipients.

[2] Section 501(a)(2)(B) of the FD&C Act (21 U.S.C. § 351(a)(2)(B)).

[3] 21 U.S.C. §§ 353b(b) and 360(b).

[4] Sections 512(a)(3) and 512(j) of the FD&C Act (21 U.S.C. § 360b(a)(3) and 360b(j)); 21 CFR part 511.

[5] Sections 512(a)(4) and (5) of the FD&C Act (21 U.S.C. § 360b(a)(4)-(5)); 21 CFR part 530.

pharmacists in state-licensed pharmacies or federal government facilities.[6] FDA is adding this guidance to provide recommendations for federally-registered facilities that operate in compliance with state laws and regulations governing drugs, pharmacy, and veterinary medicine but that may not be state-licensed pharmacies (e.g., the state has a different license for outsourcing facilities). This guidance extends FDA's enforcement discretion policies to additional types of facilities, but notes FDA generally would not intend to exercise enforcement discretion for CGMP violations at these federally-registered facilities. Federally-registered facilities manufacture or compound other drugs (such as human drugs or approved animal drugs) that are not subject to enforcement discretion policies. Applying inconsistent quality standards for different drugs made in the same federally-registered facility could complicate FDA inspections, confuse registered establishments about how and when to apply certain facility-wide CGMP requirements for human drugs or approved animal drugs manufactured at federally-registered facilities, and could confuse consumers about the expected quality of a drug they purchase from a registered establishment.

If a federally-registered outsourcing facility is also a state-licensed pharmacy and wishes to follow the recommendations in either GFI #256 and/or this guidance, it should ensure complete segregation of CGMP and non-CGMP operations (including following all relevant guidance for outsourcing facilities[7]). As outsourcing facilities are widely-understood to produce drugs under CGMP, the facility should also ensure it labels any drugs not made in accordance with CGMP in a manner that is not false or misleading (e.g., by stating the drug was not compounded under CGMP on the label or by distributing the drug under a different name than used for the facility's 503B registration).

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency'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 Agency guidances means that something is suggested or recommended, but not required.

II. Background

Under the FD&C Act, the compounding of an animal drug from BDS results in a "new animal drug" that must comply with the FD&C Act's animal drug approval, conditional approval, or indexing requirements (sections 512, 571, and 572 of the FD&C Act). In addition, 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 have adequate directions for use (section 502(f)(1) of the FD&C Act).

Animal drugs that are compounded from BDS and have not undergone FDA's premarket review process do not meet the FD&C Act's new animal drug approval or adequate directions for use requirements. GFI #256 describes the circumstances under which, at this time, FDA does not

[6] https://www.fda.gov/media/132567/download (August 2022).

[7] See, e.g., FDA's guidance "Facility Definition Under Section 503B of the Federal Food, Drug, and Cosmetic Act" (May 2018).

generally intend to take enforcement action against veterinarians, State-licensed pharmacies, and facilities operated by the Federal government compounding animal drugs from BDS for certain violations of the FD&C Act, including CGMP requirements. FDA anticipates that compounding pharmacies' home State licensing boards will provide day-to-day oversight of routine compounding practices (i.e., routine inspections for drug quality) at facilities that are not FDA-registered. However, FDA performs routine inspections and leads the oversight of drug quality at facilities registered with FDA under section 503B(b) or section 510(b) of the FD&C Act ("federally-registered facilities").

Section 503B of the FD&C Act establishes a type of federally-registered facility, called an outsourcing facility, that compounds human drugs and subjects them to various statutory conditions in order to qualify for exemptions from certain requirements of the FD&C Act, including an exemption from the new drug approval requirement for human drugs in section 505 of the FD&C Act.[8] Although section 503B does not prohibit these facilities from producing animal drugs, the exemptions in section 503B do not apply to animal drugs.[9] All animal drugs produced by these facilities from BDS that have not undergone FDA's premarket review process violate the FD&C Act's new animal drug approval and adequate directions for use requirements. For instance, although facilities that comply with section 503B and other relevant requirements of the FD&C Act can lawfully sell "office stock" for human use (i.e., distribute certain human drugs without a patient-specific prescription), they may not legally do so with animal drugs.

This draft guidance addresses animal drugs compounded from BDS in federally-registered facilities in accordance with CGMP requirements (section 501(a)(2)(B) of the FD&C Act). When animal drugs are compounded from BDS as described below, the Agency generally does not intend to take enforcement action for violations of the FD&C Act requirements for animal drug approval and adequate directions for use.

Nevertheless, FDA intends to prioritize enforcement actions under these and other provisions of the FD&C Act when the animal drugs: (1) present particular human or animal safety concerns; (2) are intended for use in food-producing animals[10] (other than antidotes, sedatives, or anesthetics described in Section III.C); (3) are copies of marketed FDA-approved or indexed drugs that lack a medical rationale describing how the compounded drug will produce a clinical difference in the identified patient (see Section III.A.5); (4) are compounded without a patient-specific prescription (other than drugs for urgent treatment needs described in Section III.B); (5) are otherwise compounded outside the circumstances described in the Policy section below; or (6) do not meet other applicable manufacturing, product quality, labeling, or packaging requirements of the FD&C Act (e.g., if the product is made under insanitary conditions or the labeling is false or misleading). FDA will make enforcement decisions on a case-by-case basis, recognizing that it needs to make the best use of limited Agency resources.

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[8] See generally, section 503B of the FD&C Act (21 U.S.C. § 353b).

[9] Section 503B(a) exempts human drugs from the new drug approval requirements of section 505, but section 503B(a) omits any reference to the new animal drug approval requirements in section 512 of the FD&C Act.

[10] Examples of food-producing animals include cattle, swine, chickens, turkeys, sheep, goats, fish (excluding ornamental and aquarium fish) and other aquatic animal species, gamebirds and wildlife raised or harvested for food, and honeybees.

III. Policy

A. Compounding for Nonfood-Producing Animals Pursuant to Patient-Specific Prescriptions by Federally-Registered Facilities

At this time, FDA generally does not intend to take enforcement action against the compounding of animal drug products from BDS for nonfood-producing animals for violations of the requirements for animal drug approval and adequate directions for use when all of the circumstances below are present:

1. The drug is compounded by or under the direct supervision of a State-licensed pharmacist under CGMP in the federally-registered facility;[11]

2. The drug is compounded in full compliance with State laws and regulations governing drugs, pharmacy, and veterinary medicine;[12]

3. All BDS, inactive ingredients, and finished drug products used in compounding meet the standards set in any applicable USP-NF monograph and comply with other FD&C Act requirements for drug components;[13]

[11] FDA generally does not intend to hold compounded animal drugs to a higher standard than the level of CGMP applicable to human drugs compounded in the same federally registered facility. FDA may choose to rely, in whole or in part, on the most recent inspection for CGMP that covered human drugs when assessing CGMP compliance for the purposes of this guidance.

[12] Federally-registered facilities are responsible for ensuring that they comply with both State laws and regulations as well as with Federal requirements, such as CGMP.

[13] The United States Pharmacopeia–National Formulary (USP–NF) is defined by the FD&C Act as an "official compendium." Drugs (including bulk drug substances and finished products) are adulterated under section 501(b) (21 U.S.C. § 351(b)) of the FD&C Act if they purport to be or are represented as a drug the name of which is recognized in an official compendium and fail to meet the standards set in the compendium for strength, quality, and purity. Adulterated drugs may not be incorporated into finished drug products. Sections 301(a), (b), (c), and (k) of the FD&C Act (21 U.S.C. § 331(a), (b), (c), and (k)). The FD&C Act has other requirements that apply to all drugs, including those used in compounding; for instance, under section 502(o) (21 U.S.C. § 352(o)), all bulk drug substances must be made in a facility registered with the FDA, otherwise they are misbranded.

4. The drug is dispensed by the facility, after receipt of a prescription for a specific patient[14] from a veterinarian acting within a valid veterinarian-client-patient relationship (VCPR), directly[15] to the prescribing veterinarian, or to the patient's owner or caretaker;

5. The compounded drug is not a copy of a marketed FDA-approved or indexed drug. Or, if it is a copy, there is a difference between the compounded drug and the FDA-approved or indexed drug(s) that will produce a clinical difference in the identified patient as determined by the treating veterinarian.

    (a) For purposes of this guidance, a drug compounded from BDS is a copy if it:

        - has the same active ingredient or active moiety[16] as a marketed FDA-approved or indexed drug, and

        - can be given by the same route of administration as the marketed FDA-approved or indexed drug.

    (b) "Clinical difference" encompasses a wide range of issues encountered in veterinary medicine, such as formulation changes to exclude ingredients in the approved product that are harmful to a particular patient or their species; strength or concentration changes to accommodate wide variations in patient size; and changes in flavoring or dosage form needed to achieve patient compliance or protect individuals administering the drug. It does not include pricing differences (e.g., compounding to offer a less expensive product).

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[14] For purposes of this guidance, a patient-specific prescription is one that identifies the specific animal patient to be treated (e.g., patient name or identification number, room or cage number, etc.). A patient may be a single animal or an identifiable group of animals of the same species consisting of a specific number of animals in an identified location (e.g., all cats in isolation ward X (# cats), all dogs in kennel Y (# dogs), or all horses in stable Z (# horses)). The group and location should be adequately described such that an objective observer could positively ascertain whether an animal is part of the group at the time of prescribing. A group prescription authorizes the treatment of each and every animal in the group with the drug because all the animals have the same medical need at the time the prescription is written. If the animals in a group have different medical needs, patient-specific prescriptions should be used for individual animals. FDA generally considers drugs compounded for a group of animals to be office stock if, based on the number of animals, the indication, the quantity of drugs prescribed, and any other relevant circumstances, it is implausible that only the specific identified group of animals will be treated with the compounded animal drugs. FDA considers office stock distributed under the guise of patient-specific prescriptions to be a serious concern.

[15] The enforcement discretion policy described in this guidance does not apply to compounded drugs that are dispensed or transferred to a third party such as a distributor or retailer, or by a pharmacy to a veterinarian who did not write the prescription.

[16] Active moiety means the molecule or ion, excluding those appended portions of the molecule that cause the drug to be an ester, salt (including a salt with hydrogen or coordination bonds), or other noncovalent derivative (such as a complex, chelate, or clathrate) of the molecule responsible for the physiological or pharmacological action of the drug substance (21 CFR 314.3). For example, for the active ingredients erythromycin stearate, erythromycin ethylsuccinate, and erythromycin lactobionate the active moiety is erythromycin.

(c) When compounding a copy, the pharmacist should maintain a record of the medical rationale describing the clinical difference, either by retaining a copy of a prescription on which the veterinarian has noted the medical rationale describing the clinical difference, or by contacting the veterinarian to obtain their medical rationale describing the clinical difference and noting it on the prescription or a document kept with it. It is not possible to offer exhaustive guidance about the types of changes that result in a clinical difference to an identified individual patient. Similarly, it is not possible to offer exhaustive guidance about the variety of applicable medical rationales. FDA generally does not intend to question prescriber determinations that are documented in a prescription or notation. However, we do intend to consider whether a prescription or notation relied upon by a compounder both documents that the determination was made and contains a medical rationale describing the clinical difference. (See GFI #256 for examples.)

6. If the compounded animal drug has any of the same active ingredient moiety(ies) as one or more marketed FDA-approved or indexed drugs, the compounder has determined and documented the reason(s) why none of these drugs can be used as the source(s) of the active ingredients.[17] (See GFI #256 for examples);
7. Upon becoming aware of any adverse event[18] or product defect[19] associated with an animal drug compounded from a BDS, the federally-registered facility reports the event on Form FDA 1932a, which is available online, within 15 business days;
8. The label of the compounded drug identifies the specific patient to be treated, such as the name of the patient, identifier for the individual animal (e.g., horse in stall X), or identification of a group of animals that are all being treated for the same indication (e.g., all dogs in shelter kennel X (# dogs));[20]
9. The labeling of the compounded drug includes all of the following, in addition to any other information required by State law:

    - name of drug;
    - strength of drug;
    - species of the patient;

[17] While the FD&C Act prohibits the extralabel use of conditionally approved and indexed animal drugs, under this guidance, at this time, FDA generally does not intend to take enforcement action when conditionally approved and indexed animal drugs are used as the source of the starting material for compounded animal drugs.

[18] Adverse events include those occurring in animals, reports of lack of effectiveness, or adverse events occurring in humans from product exposure.

[19] A product defect includes product quality issues in the drug product, product components, or product labeling. Examples of product defects include sterility failures, endotoxin failures, media fill failures, suspected cross contaminations, and incorrect potency.

[20] Providing the patient identification on the label itself assists FDA in ascertaining whether the compounded drug is office stock and helps prevent its use in animals other than the identified patient.

- indication for which the drug is being prescribed;[21]
- dosing (dosing information should be specific to the individual patient, providing the amount of drug needed per administration and the frequency of administration. FDA does not consider "use as directed" or similar statements to constitute dosing for the purposes of this guidance.);
- the name, address, and contact information for the compounder and name of prescribing veterinarian;
- a beyond use date or expiration date;
- the statement, "Report suspected adverse reactions to [name of compounder] and to FDA using online Form FDA 1932a";
- the statement, "This is a compounded drug. Not an FDA approved or indexed drug."; and
- the statement, "Caution: Federal law restricts this drug to use by or on the order of a licensed veterinarian.";[22] and

10. The drug is compounded in accordance with CGMP, the facility is registered with FDA as a producer of animal drugs, and, if produced in batch sizes for more than a single patient more than once, the drug is listed with FDA.[23]

B. Compounding for Nonfood-Producing Animals Without Patient-Specific Prescriptions ("Office Stock") by Federally-Registered Facilities

At this time, FDA generally does not intend to take enforcement action against the compounding of drug products from BDS as office stock for nonfood-producing animals for violations of the requirements for animal drug approval and adequate directions for use when all of the circumstances below are present:

1. The drug is compounded by or under the direct supervision of a state-licensed pharmacist under CGMP in the federally-registered facility;[24]

[21] FDA does not consider "use as directed" or similar statements to constitute an indication for which the drug is to be used.

[22] Section 503(f)(4) of the FD&C Act (21 U.S.C. § 353(f)(4)); 21 CFR 201.105(b)(1).

[23] See Section 510 of the FD&C Act (21 U.S.C. § 360); 21 CFR 207.17. The period specified in 21 CFR 207.57(b) for updating drug listings is once every six months. Facilities should register using the appropriate business operation(s) (e.g., "Animal Drug Compounding in 503B Human Drug Outsourcing Facility" or "Manufacture"). When submitting labeling, placeholders identifying patient-specific information that must be obtained from veterinarians may be used (e.g., indication, dosing, patient identifier, prescribing veterinarian).

[24] FDA generally does not intend to hold compounded animal drugs to a higher standard than the level of CGMP applicable to human drugs compounded in the same federally registered facility. FDA may choose to rely, in whole or in part, on the most recent inspection for CGMP that covered human drugs when assessing CGMP compliance for the purposes of this guidance.

2. The drug is compounded in full compliance with State laws and regulations governing drugs, pharmacy, and veterinary medicine;

3. All BDS, inactive ingredients, and finished drug products used in compounding meet the standards set in any applicable USP-NF monograph and comply with other FD&C Act requirements for drug components;

4. The drug is intended for use in a nonfood-producing species and is compounded from a BDS listed on FDA's "List of Bulk Drug Substances for Compounding Office Stock Drugs for Use in Nonfood-Producing Animals" described in GFI #256;[25]

5. The drug is distributed directly[26] from the compounder to a veterinarian or health care facility, such as a veterinary hospital or clinic, where the drug is administered to a patient, or dispensed to a caretaker of the patient;

6. Upon becoming aware of any adverse event or product defect associated with an animal drug compounded from a BDS, the federally-registered facility that compounded the drug reports the event on Form FDA 1932a, which is available online, within 15 business days;

7. The labeling of the compounded drug includes all of the following:
    - name of drug;
    - strength of drug;
    - the species of the patient(s);
    - the indication(s) for which the drug will be used;
    - the name, address, and contact information for the compounder;
    - the name, address, and contact information for the veterinarian ordering the office stock;
    - a beyond use date or expiration date;
    - the statement, "Report suspected adverse reactions to [name of compounder] and to FDA using online Form FDA 1932a";
    - the statement, "This is a compounded drug. Not an FDA approved or indexed drug.";

[25] Additionally, FDA will extend its policy regarding nominated bulk drug substances under review as described in GFI #256 to federally-registered facilities.

[26] The enforcement discretion policy described in this guidance does not apply to compounded drugs that are transferred to a third party such as a distributor, retailer, or veterinarian at another physical location.

- the statement, "Not for use in food-producing animals"; and
- the statement, "Caution: Federal law restricts this drug to use by or on the order of a licensed veterinarian."[27]; and

8. The drug is compounded in accordance with CGMP, the facility is registered with FDA as a producer of animal drugs,[28] and the drug is listed with FDA.[29]

C. Compounding for Food-Producing Animals: Drugs for Use as Antidotes for Food-Producing Animals or Sedatives and Anesthetics for Free-Ranging Wildlife Species Produced by Federally-Registered Facilities

At this time, FDA generally does not intend to take enforcement action against the compounding of drug products from BDS intended for use as antidotes for treating toxicoses in food-producing animals or for use as sedatives or anesthetics in free-ranging wildlife species for violations of the animal drug approval and adequate directions for use requirements when all of the circumstances below are present:

1. The drug is compounded by or under the direct supervision of a State-licensed pharmacist under CGMP in a federally-registered facility;

2. The drug is compounded in full compliance with State laws and regulations governing drugs, pharmacy, and veterinary medicine;

3. All BDS, inactive ingredients, and finished drug products used in compounding meet the standards set in any applicable USP-NF monograph and comply with other FD&C Act requirements for drug components;

4. The drug is compounded from a BDS on the "List of Bulk Drug Substances for Compounding Drugs for Use in Food-Producing Animals or Free-Ranging Wildlife Species as described in GFI 256;[30]

5. The prescribing veterinarian has a valid VCPR and establishes and documents a scientifically based withdrawal time that ensures residues of the: (1) antidote, or (2) sedative or anesthetic are not present in the animal at the time of slaughter or harvest or the veterinarian ensures the animal does not enter the food supply[31];

6. The prescribing veterinarian ensures that the animal does not enter the food supply too soon or at all. This can be done by confining the treated animal for the needed

[27] Section 503(f)(4) of the FD&C Act (21 U.S.C. § 353(f)(4)); 21 CFR 201.105(b)(1).

[28] Using the Business Operation as appropriate (e.g., "Animal Drug Compounding in 503B Human Drug Outsourcing Facility" or "Manufacture").

[29] Each animal drug sold as office stock should have an NDC and be drug listed as described in 21 CFR Part 207.

[30] FDA will extend the same policy for nominated bulk drug substances under review as described in GFI #256 to federally-registered facilities.

[31] Section 402(a) of the FD&C Act (21 U.S.C. § 342(a)); 21 CFR 530.20(b)(2).

withdrawal time or identifying the animal(s) that has been treated. For example, for free-ranging wildlife the animal could be identified with a tag containing language such as "DO NOT CONSUME if harvested before [enter date after completed withdrawal period]; Call [enter phone number of veterinarian or animal health professional].";

7. The drug is distributed directly from the compounder to a veterinarian or health care facility, such as a veterinary hospital or clinic, where the drug is administered to a patient, or dispensed to a caretaker of the patient;[32]

8. Upon becoming aware of any adverse event or product defect associated with a drug compounded from a BDS, the federally-registered facility reports the event on Form FDA 1932a, which is available online, within 15 business days;

9. The labeling of the antidote, sedative, or anesthetic includes all of the following:
    - name of drug;
    - strength of drug;
    - the species of the patient(s) and indications for which the drug will be used;
    - the name, address, and contact information for the compounder;
    - the name, address, and contact information for the prescribing veterinarian;
    - a beyond use date or expiration date;
    - prescribing veterinarian-determined withdrawal time;
    - the statement, "Report suspected adverse reactions to [name of compounder] and to FDA using online Form FDA 1932a";
    - the statement, "This is a compounded drug. Not an FDA approved or indexed drug."; and
    - the statement, "Caution: Federal law restricts this drug to use by or on the order of a licensed veterinarian."[33]; and

10. The drug is compounded in accordance with CGMP, the facility is registered with FDA as a producer of animal drugs, and if produced in batch sizes for more than a single patient more than once, the drug is listed with FDA.

[32] The enforcement discretion policy described in this guidance does not apply to compounded drugs that are transferred to a third party such as a distributor, retailer, or veterinarian at another physical location.

[33] Section 503(f)(4) of the FD&C Act (21 U.S.C. § 353(f)(4)); 21 CFR 201.105(b)(1).