

Compounding Animal Drugs from Bulk Drug Substances

Guidance for Industry

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For further information regarding this document, contact AskCVM@fda.hhs.gov.

Additional copies of this guidance document may be requested from the Policy and Regulations Staff (HFV-6), Center for Veterinary Medicine, Food and Drug Administration, 7500 Standish Place, Rockville, MD 20855, 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 <https://www.regulations.gov>.

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Compounding Animal Drugs from Bulk Drug Substances

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This guidance represents the Food and Drug Administration's (FDA or Agency) current thinking 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 guidance describes 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 by or under the direct supervision of:

- Veterinarians, or
- Pharmacists in either State-licensed pharmacies or Federal facilities (i.e., facilities operated by the Federal government).²

This guidance does not apply to animal drugs compounded for use in investigations of new animal drugs or to animal drugs compounded from FDA-approved animal or human drugs, which are considered legal extralabel uses of such drugs.³

The contents of this document do not have the force and effect of law and are not meant to bind the public in any way, unless specifically incorporated into a contract. This document is intended only to provide clarity to the public regarding existing requirements under the law. FDA's guidance documents should be viewed only as recommendations, unless specific regulatory or statutory

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." Title 21 of the Code of Federal Regulations, section 210.3(b)(7) (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 Throughout this guidance, the terms "pharmacists," "pharmacies," and "veterinarians" refer to those persons or entities that are State-licensed and operate in full compliance with State laws and regulations governing their practice.

³ Section 512(a)(3), (4), and (5) and 512(j) of the FD&C Act (21 U.S.C. § 360b(a)(3)-(5), 360b(j)) and 21 CFR parts 511 (investigational use) and 530 (extralabel use)

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requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

As described below in section [II. Background](#), animal drugs compounded from bulk drug substances by pharmacists and veterinarians do not meet certain important requirements of the Federal Food, Drug, and Cosmetic Act (FD&C Act). To be legally marketed under the animal drug approval requirements of the FD&C Act, an approval, conditional approval, or listing on the Index of Legally Marketed Unapproved New Animal Drugs for Minor Species⁴ is required, and compounded drugs do not go through any of these pre-market review processes. Further, all animal drugs are required to, among other things, be made in accordance with current good manufacturing practice (CGMP) requirements and have adequate directions for use, requirements not met by compounded drugs.⁵ Thus, drugs compounded from bulk drug substances violate the FD&C Act because they are not approved or indexed, are not made according to CGMP, and cannot satisfy the FD&C Act's adequate directions for use provision (which requires, among other things, that a prescription drug have FDA-approved labeling). However, FDA has generally refrained from taking enforcement action against animal drugs compounded from bulk drug substances under certain circumstances when no other medically appropriate treatment options exist. This guidance continues this practice to balance FDA's concerns about the risks of animal drugs compounded from bulk drug substances, which have not gone through Agency premarket review, with the need for such drugs when no FDA-approved or indexed drug is medically appropriate to treat the animal. This guidance is intended to provide additional information and clarify FDA's current thinking about animal drug compounding from bulk drug substances.

At this time and based on our current understanding of the risks of animal drugs compounded from bulk drug substances, FDA generally does not intend to take enforcement action for violations of the FD&C Act's requirements for approval, adequate directions for use, and CGMP for compounding of products under the circumstances below. The policies described in this document are intended to protect human and animal health by limiting the use of animal drugs compounded from bulk drug substances to when a veterinarian, acting within a valid veterinarian-client-patient relationship (VCPR),⁶ determines there is no medically appropriate human or animal drug that is FDA-approved,⁷ conditionally approved, or indexed to treat the animal (referred to as "FDA-approved or indexed drugs" in this document). These policies are also intended to focus FDA's enforcement activities on animal drugs compounded from bulk drug substances that present the most significant concerns, including compounded drugs that:

⁴ Sections 512, 571, and 572 of the FD&C Act (21 U.S.C. §§ 360b, 360ccc, 360ccc-1)

⁵ Section 501(a)(2)(B) of the FD&C Act (21 U.S.C. § 351(a)(2)(B)), 21 CFR parts 210 and 211, and section 502(f)(1) of the FD&C Act (21 U.S.C. § 352(f)(1))

⁶ A valid VCPR is a relationship in which, among other things, the veterinarian: (1) has assumed responsibility for making medical judgments concerning the health of the animal patient and the need for medical treatment; (2) is familiar enough with the animal patient to make a general diagnosis of the medical condition; and (3) is readily available for follow-up should an adverse reaction occur or the prescribed therapy is not effective. For a complete definition of VCPR, see 21 CFR 530.3(i).

⁷ Unless explicitly limited to "animal drugs," the term "FDA-approved drugs" includes FDA-approved human drugs, FDA-approved animal drugs, conditionally approved animal drugs, and licensed human biologics.

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- present particular human or animal safety concerns;
- are intended for use in food-producing animals⁸;
- are copies of marketed FDA-approved or indexed drugs⁹; or
- are compounded without a patient-specific prescription (i.e., office stock).

FDA will make enforcement decisions on a case-by-case basis, recognizing that it needs to make the best use of limited Agency resources.

II. BACKGROUND

A. Legal Marketing Pathways for Animal Drugs

To be legally marketed, animal drugs, with few exceptions, must be approved, conditionally approved, or indexed by FDA.¹⁰

The FDA approval process provides important protections for humans and animals. A drug company (sponsor) seeking FDA approval of an animal drug application must submit data and information that demonstrate, among other things, that the animal drug is safe and effective (or in the case of a generic drug, that the drug is bioequivalent to an already FDA-approved drug), properly manufactured, and accurately labeled.¹¹ If the drug is for use in food-producing animals, the sponsor must submit data regarding the drug's potential for creating harmful residues in the meat, milk, eggs, and other edible products from treated animals.¹²

FDA's application review encompasses, among other things, the specific active and inactive ingredients to be used; manufacturing methods; and labeling, including the drug's indications, intended species, warnings, safety information, and other conditions of use. FDA approval means that FDA has determined that the data demonstrate that the approved animal drug is safe, effective, properly manufactured to ensure drug quality, and adequately labeled. For drugs approved for food-producing animals, labeling must provide data-based residue tolerances; withdrawal, withholding, and/or discard times; and other conditions of use needed to prevent products from

⁸ 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.

⁹ For purposes of this guidance, a drug is "marketed" if the drug manufacturer is making and offering the drug for sale. For animal drugs that are temporarily in shortage, FDA will apply its process for mitigating shortages. Actions may include working with drug manufacturers and others in the animal health industry, speeding up the animal drug review and approval process, encouraging sponsors of alternate products to increase production, or refraining from taking action against imports of foreign-approved versions of the drug product. <https://www.fda.gov/animal-veterinary/product-safety-information/animal-drug-shortage-information>

¹⁰ Animal drugs that are not FDA-approved, conditionally approved, or indexed are considered "unsafe" and, therefore, "adulterated" under sections 512(a)(1) and 501(a)(5) of the FD&C Act (21 U.S.C. §§ 360b(a)(1) and 351(a)(5)).

¹¹ Sections 512(b)(1), (c)(2), (d) and (n) of the FD&C Act (21 U.S.C. §§ 360b(b)(1), (c)(2), (d) and (n)); 21 CFR 514.1(b)

¹² See footnote 11, especially 21 CFR 514.1(b)(7).

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treated animals that contain harmful residues from entering the food supply.¹³

In addition to pre-market review, FDA-approved animal drugs are subject to requirements once they are on the market. For instance, sponsors must submit reports of adverse events, product defects, and manufacturing quality, and provide copies of any post-approval laboratory or clinical studies conducted or obtained by the sponsor throughout the lifetime of the product.¹⁴ This information allows FDA to continue to monitor the safety and effectiveness of the drug after approval.

The conditional approval¹⁵ and indexing¹⁶ processes provide alternative pathways to legal marketing that address the specific challenges associated with full FDA approval for drugs intended for minor uses,¹⁷ minor species,¹⁸ or for certain other new animal drugs. Like the full approval process, these provisions protect human and animal health by requiring FDA review of information regarding safety, effectiveness, manufacturing, and labeling before a drug that qualifies for these pathways can be legally marketed. They also provide for FDA to monitor safety and effectiveness after the product is on the market.

B. Animal Drugs Compounded from Bulk Drug Substances

The law permits compounding of an animal drug when the source(s) of the active ingredient(s) for compounding is a finished FDA-approved drug(s) and not a bulk drug substance. Specifically, the extralabel use provisions of the FD&C Act permit the compounding of animal drugs made from FDA-approved animal or human drugs, provided the conditions for legal extralabel use described in the FD&C Act and FDA's extralabel use regulations are met.¹⁹ These regulations state that, “[n]othing in this part shall be construed as permitting compounding from bulk drugs.”²⁰

¹³ Sections 512(a)(1)(A) and (B) of the FD&C Act (21 U.S.C. §§ 360b(a)(1)(A) and (B))

¹⁴ Section 512(l) of the FD&C Act (21 U.S.C. § 360b(l)), 21 CFR 514.80

¹⁵ “Conditional approval” allows the sponsor to make a drug for a minor use or minor species and certain other new animal drugs available before collecting all effectiveness data necessary for approval of a new animal drug application (NADA) under section 512 of the FD&C Act, but after proving the drug is safe in accordance with the full FDA approval standard and showing that there is a reasonable expectation of effectiveness. FDA may permit the drug sponsor to keep the conditionally approved new animal drug on the market for up to 5 years, through annual renewals, while collecting the remaining required effectiveness data.

¹⁶ “The Index” allows drug companies to market certain unapproved drugs for minor species. The Index is limited to drugs intended for use in nonfood-producing, minor species and some early non-food life stages of food-producing minor species.

¹⁷ The term “minor use” means the intended use of a drug in a major species for an indication that occurs infrequently only in a small number of animals, annually, or in limited geographical areas. Section 201(pp) of the FD&C Act (21 U.S.C. § 321(pp)).

¹⁸ The term “minor species” means animals other than humans that are not major species. Section 201(oo) of the FD&C Act (21 U.S.C. § 321(oo)). Major species are dogs, cats, horses, pigs, cattle, turkeys, and chickens. Section 201(nn) of the FD&C Act ((21 U.S.C. § 321(nn)).

¹⁹ Sections 512(a)(4) and (5) of the FD&C Act (21 U.S.C. § 360(a)(4) and (5)) and 21 CFR part 530

²⁰ 21 CFR 530.13(a)

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The FD&C Act does not generally distinguish between compounding animal drugs from bulk drug substances and other methods of animal drug manufacturing.²¹ The FD&C Act's requirements regarding drug approval, drug manufacturing, product quality, and labeling apply to animal drugs compounded from bulk substances, just as they apply to drugs manufactured by pharmaceutical companies. As explained above, drugs compounded from bulk drug substances violate the FD&C Act because they are not approved or indexed, are not made according to CGMP, and cannot satisfy the FD&C Act's adequate directions for use provision (which requires, among other things, that a prescription drug have FDA-approved labeling).

When a drug is compounded from bulk drug substances using the same active ingredient that is in an approved or indexed drug, it is not the equivalent of the FDA-approved or indexed brand-named drug, not the equivalent of an FDA-approved generic drug, and cannot be presumed to have the same effect as the approved or indexed drug. When FDA approves or indexes a drug, FDA review and approval or index listing covers not only the active ingredient but the finished product, with specific active and inactive ingredients, sources of ingredients, manufacturing processes, drug specifications, and labeling. All of these factors are critical in determining the safety and effectiveness of a drug product prior to approval. Further, the approved animal drug becomes part of FDA's post-approval monitoring and pharmacovigilance programs, where FDA monitors adverse events, product defects, prescription drug advertising, and changes in the manufacturing and labeling of the approved animal drug. Because compounded animal drugs are not FDA-approved, they do not have these same assurances of safety, efficacy, and quality as FDA-approved and indexed products.

III. POLICY

Although numerous drugs are FDA-approved or indexed for use in animals, there are many different species of animals, each with a variety of diseases and conditions for which there are no FDA-approved or indexed drugs. While there are cases in which FDA-approved animal or human drugs can be used to treat an animal under the extralabel use provisions of the FD&C Act and related regulations, FDA recognizes that there are circumstances in which no FDA-approved or indexed drug (including the extralabel use of an FDA-approved animal or human drug) can be used to treat an animal with a particular condition. In those limited circumstances, an animal drug compounded from bulk drug substances may be a medically appropriate treatment.

This guidance balances FDA's concerns about the safety, effectiveness, and quality of animal drugs compounded from bulk drug substances, which have not gone through Agency premarket review, with the need for such drugs when no FDA-approved or indexed drug is medically appropriate to treat the animal.²² Because of the safety and effectiveness benefits and protections

²¹ Sections 503A and 503B of the FD&C Act (21 U.S.C. §§ 353a, 353b), which provide certain statutory exemptions for compounded human drugs, do not apply to drugs compounded for use in animals.

²² The extralabel use provisions of the FD&C Act apply to human drugs approved under section 505 of the FD&C Act and animal drugs approved under section 512 of the FD&C Act. They do not provide for extralabel use of conditionally approved or indexed animal drugs, or human biological products licensed by FDA under section 351 of the Public Health Service Act. However, at this time FDA generally does not intend to take action against extralabel use of these drugs to compound animal drugs, which we believe is a less risky alternative to using drugs compounded

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of the pre-market review process and post-market monitoring of FDA-approved and indexed drugs, veterinarians should only use drugs compounded from bulk drug substances if FDA-approved or indexed drugs are not medically appropriate to treat the animal.

This guidance describes:

- The types of drugs compounded from bulk drug substances that FDA has determined present the greatest risk to human and animal health and intends to make priorities for enforcement action; and
- The circumstances under which, at this time, FDA does not generally intend to take enforcement action against drugs compounded from bulk drugs substances for violations of the FD&C Act's requirements for approval, adequate directions for use, and CGMPs.

These circumstances are separately described below for drugs compounded:

- to fill patient-specific prescriptions for nonfood-producing animals (see section [A. Compounding for Nonfood-Producing Animals: Patient-Specific Prescriptions](#));
- for office stock for nonfood-producing animals (see section [B. Compounding for Nonfood-Producing Animals: Without Patient-Specific Prescriptions \("Office Stock"\)](#)); and
- for food-producing animals (section [C. Compounding for Food-Producing Animals: Drugs for Use as Antidotes for Food-Producing Animals or Sedatives and Anesthetics for Free-Ranging Wildlife Species](#)).

These policies are intended to address FDA's concerns about the compounding of animal drugs from bulk drug substances, including significant concerns with such drugs when they:

- Present particular animal or human safety concerns. Examples include superpotency, microbial contamination, and drug formulations that present safety risks for the treated animals or for people handling or administering the animal drug. To help FDA identify compounded drugs that present safety concerns and to prevent future harm, the FDA encourages veterinarians, pharmacists, and animal owners to report adverse events associated with compounding animal drugs from bulk drug substances on FDA's website using [Form FDA 1932a](#).
- Are intended for use in food-producing animals. Drugs compounded from bulk drug substances for use in food-producing animals present safety concerns because of the potential for harmful residues in food from treated animals. However, FDA recognizes that in some cases of toxicoses in food-producing animals, which can be life-threatening and may affect large groups of animals, an antidote compounded from a bulk drug substance may be the only treatment option and may be urgently needed to prevent animal suffering or death. FDA also recognizes the need for wildlife health professionals to have immediate access to some sedatives and anesthetics compounded from bulk drug substances for the capture and immobilization of free-ranging wildlife. As described below in section

from bulk drug substances.

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[C. Compounding for Food-Producing Animals: Drugs for Use as Antidotes for Food-Producing Animals or Sedatives and Anesthetics for Free-Ranging Wildlife Species](#), this guidance describes circumstances in which, at this time FDA generally does not intend to take enforcement action for limited compounding of certain antidotes for food-producing animals, and sedatives and anesthetics for free-ranging wildlife.²³ These drugs are identified by the veterinary community, reviewed by FDA and available on the FDA website, which includes only bulk substances to compound drugs for antidotes, and sedatives and anesthetics that cannot be met by onlabel or extralabel use of an FDA-approved or indexed drug.²⁴ When using these drugs, we expect the prescribing veterinarian, acting within a valid VCPR, to establish scientifically-based withdrawal, withholding, and discard times to ensure that animals treated with these drugs do not contain residues of the antidote, sedative, or anesthetic,²⁵ or alternatively, to ensure that the treated animals do not enter the food supply.

- Are copies of a marketed FDA-approved or indexed drug. FDA supports increased availability of legally marketed animal drugs that have demonstrated that they are safe and effective, properly manufactured to ensure drug quality, and accurately labeled. Compounding copies of such drugs presents a disincentive to submit a new animal drug application, an abbreviated new animal drug application for generic animal drugs, an application for conditional approval, or a request for indexing, further reducing the availability of legally marketed animal drugs. As described below in section [A. Compounding for Nonfood-Producing Animals: Patient-Specific Prescriptions](#), this guidance explains the circumstances in which FDA generally does not intend to take enforcement action at this time for compounded drugs, including limited copies, dispensed under a patient-specific prescription.
- Are sold as office stock (as opposed to dispensed by a pharmacy upon receipt of a prescription for an identified patient²⁶). The Agency is concerned that compounded office stock potentially exposes large numbers of animals to drugs of unproven safety, effectiveness, and quality. However, FDA recognizes that in some limited cases an animal drug is urgently needed, and the time needed to compound a drug in response to an

²³ In emergency situations where the need for euthanasia or depopulation drugs for food-producing species cannot be met using an FDA-approved or indexed drug or by other non-drug depopulation methods, veterinarians should contact CVM's Emergency Response Coordinators directly at CVMCERTINV@fda.hhs.gov. FDA will work with our public health partners to consider the use of drugs compounded from bulk drug substances on a case-by-case basis.

²⁴ See FDA's "List of Bulk Drug Substances for Compounding Drugs for Use in Food-Producing Animals or Free-Ranging Wildlife Species," available at <https://www.fda.gov/animal-veterinary/animal-drug-compounding/list-bulk-drug-substances-compounding-drugs-use-food-producing-animals-or-free-ranging-wildlife>.

²⁵ Sources of appropriate scientific information for setting withdrawal, withholding, and discard times could include, for example, information from the Food Animal Residue Avoidance & Depletion Program (FARAD) (www.farad.org), published textbooks, and peer-reviewed published journal articles. As of the date of this guidance, there are no approved, conditionally approved, or indexed antidotes for food-producing animals, which means that food containing residues of an antidote is adulterated under section 402(a) of the FD&C Act (21 U.S.C. § 342(a)).

²⁶ For purposes of this guidance, a prescription includes the species of the animal patient, and identifying information about the animal patient (e.g., patient name or identification number, room or cage number, etc.), and otherwise complies with applicable State law. A patient may be a single animal or a group of animals in a specific, identified location (e.g., cats in isolation ward X, dogs in kennel Y, or horses in stable Z).

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individual patient prescription may result in animal suffering or death. As described below in section [B. Compounding for Nonfood-Producing Animals: Without Patient-Specific Prescriptions \(“Office Stock”\)](#), this guidance explains the limited circumstances in which FDA generally does not intend to take enforcement action for compounding office stock at this time. Drugs for use to compound as office stock are nominated by the veterinary community, reviewed by FDA, and available on the FDA website, which includes bulk substances to compound drugs for urgent treatment needs that cannot be met by onlabel or extralabel use of an FDA-approved or indexed drug.²⁷

When pharmacies and veterinarians compound animal drugs from bulk drug substances as described below, the Agency generally does not intend to take enforcement action for violations of the FD&C Act’s requirements for animal drug approval; adequate directions for use; and CGMP. Nevertheless, FDA intends to prioritize enforcement of these provisions when: (1) the animal drugs are compounded outside the circumstances described below; (2) the compounded drugs present particular human or animal safety concerns; or (3) the compounded drugs do not meet other 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 ordinarily rely on compounding pharmacies’ home State licensing boards to provide day-to-day oversight of routine compounding practices (i.e., routine inspections for drug quality) but may provide concurrent oversight of compounding practices when considered appropriate by the Agency. Should FDA have cause for concern, the Agency may also refer a case to the appropriate State licensing board(s).

A. Compounding for Nonfood-Producing Animals: Patient-Specific Prescriptions

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

1. The drug is compounded by or under the direct supervision of
 - a veterinarian, or
 - a pharmacist in a State-licensed pharmacy or Federal facility;
2. The drug is compounded in full compliance with State laws and regulations governing drugs, pharmacy, and veterinary medicine;
3. All bulk drug substances, 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;²⁸

²⁷ See FDA’s “List of Bulk Drug Substances for Compounding Office Stock Drugs for Use in Nonfood-Producing Animals,” available at <https://www.fda.gov/animal-veterinary/animal-drug-compounding/list-bulk-drug-substances-compounding-office-stock-drugs-use-nonfood-producing-animals>.

²⁸ 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

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4. The drug is dispensed by—
 - (a) the pharmacy, after receipt of a prescription for a specific patient from the veterinarian acting within a valid VCPR, directly to the prescribing veterinarian or to the patient’s owner or caretaker or,
 - (b) the veterinarian to the owner or caretaker of a patient in his or her practice, or to another veterinarian in his or her practice located in the same physical location. 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;
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 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 bulk drug substance is a copy if it:
 - has the same active ingredient or active moiety²⁹ 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).
 - (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, or by contacting the veterinarian to obtain their medical rationale and noting it on the

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.

²⁹ 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.

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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. For example, the notation should provide a brief statement of the medical rationale that contains the basic facts underlying the determination:

- “Patient is allergic to ingredient [X] in approved product.”
 - FDA does not generally intend to question the veterinarian’s determination the specific patient has an allergy to X. The allergy to X constitutes the medical rationale describing the clinical difference between the compounded and approved product. Identifying the specific allergenic ingredient (“X”) is an important part of the medical rationale because its presence in the approved product and absence in the compounded product produces the clinical difference in the individual patient.
- “[Ingredient name] in approved product is toxic to this species.”
 - FDA does not generally intend to question the veterinarian’s determination that an ingredient is toxic to a particular species and does not expect literature references or other information in the rationale. FDA would dispute this determination only in limited circumstances, e.g., if there was significant evidence to the contrary such as the presence of the specific ingredient in the same or greater concentration in FDA-approved products for that species.
- “Patient would require too many tablets of the approved product.”
 - FDA does not generally intend to question the veterinarian’s determination the patient will need to be administered an unreasonable number of tablets for the patient and, therefore, requires a prescription that significantly reduces the number of tablets administered.
- “Patient requires dose that would require a fraction of the approved tablet, and tablet is not scored to accomplish this fractionated dose.”
 - FDA does not generally intend to question the veterinarian’s determination that the patient will need to be administered a dose requiring a fraction of the approved tablet for the patient and the tablet is not scored to accomplish this fractionated dose. In this case, the prescription should be for a single, corresponding lower dose.
- “Patient cannot safely be pillled with the approved capsule.”

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- FDA does not generally intend to question the veterinarian's determination the patient will not accept the specified dosage form if the prescription is for a different dosage form.

The following are examples that FDA would not consider medical rationales:

- “The compounded drug is less expensive.”
 - Economic consideration is not a *medical* rationale and would not be considered an acceptable reason for compounding a copy of an approved drug.
- “Prefer [compounded drug/compounder].”
 - The preferences of the prescriber or owner is not a medical rationale and would not be considered an acceptable reason for compounding a copy of an approved drug.
- “Need half strength” (Approved product is 10 mg/ml solution, prescription is written for 10 ml dose of 5 mg/ml solution)
 - The statement “need half strength” on its own is a conclusion and not a medical rationale *describing the clinical difference*. In this case, a prescription for a 5 ml dose of the 10 mg/ml approved product would deliver the same amount of active ingredient. The statement does not explain how the compounded product would produce a clinical difference in the individual patient. By contrast, a statement such as, “need half strength to reduce irritation upon application,” would explain the clinical difference and why a lower quantity of the approved drug could not be used.

If the prescribing veterinarian is compounding the drug, the medical rationale should be noted in the patient's medical record;

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.³⁰ These reasons may include, for example:
 - The chemical properties of the FDA-approved or indexed drug(s) prevent its practical and effective use in the compounding of a specific drug. For example, it may not be possible to compound an ophthalmic solution from an approved topical cream, or it may not be possible to compound a sterile injectable from a non-sterile dosage form;
 - An inactive ingredient in the FDA-approved or indexed drug(s) is toxic to the target species and cannot be readily separated. For example, a compounded drug is ordered for a dog, but the only drug product(s) containing that active moiety also

³⁰ 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.

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contains the inactive ingredient xylitol, which is toxic to dogs; or

- The FDA-approved or indexed drug(s) that contains that active moiety is not available for compounding. For example, a compounding pharmacy receives a prescription, but all drug products containing that active ingredient are only being sold directly to veterinarians by the sponsor(s)/distributor(s), and, therefore, the pharmacy is unable to purchase the products.
7. Upon becoming aware of any adverse event³¹ or product defect³² associated with an animal drug compounded from a bulk drug substance, the pharmacist or veterinarian who compounded the drug reports the event on [Form FDA 1932a](#), which is available online, within 15 business days; and
 8. 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;
 - patient identification, 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 (e.g., dogs in shelter kennel X);
 - the name, address, and contact information for the compounding pharmacy or veterinarian and name of prescribing veterinarian;
 - a beyond use date;
 - the statement, “Report suspected adverse reactions to the [pharmacist or veterinarian who compounded the drug] 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

B. Compounding for Nonfood-Producing Animals: Without Patient-Specific Prescriptions (“Office Stock”)

At this time, FDA generally does not intend to take enforcement action against the compounding of animal drugs from bulk drug substances as office stock for nonfood-producing animals for

³¹ Adverse events include those occurring in animals, reports of lack of effectiveness, or adverse events occurring in humans from product exposure.

³² 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.

³³ 21 CFR 201.105(b)(1)

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violations of the requirements for animal drug approval, adequate directions for use, and CGMP when all of the circumstances below are present:

1. The drug is compounded by or under the direct supervision of
 - a veterinarian, or
 - a pharmacist in a State-licensed pharmacy or a Federal facility;
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](#)" described in the Appendix to this guidance;
3. The drug is compounded in full compliance with State laws and regulations governing drugs, pharmacy, and veterinary medicine. All bulk drug substances, 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 veterinarian who stocks the drug dispenses or transfers it only to the owner or caretaker of the animal patient or to another veterinarian in the same practice.

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;

5. Upon becoming aware of any adverse event or product defect associated with an animal drug compounded from a bulk drug substance, the pharmacist or veterinarian that compounded the drug reports the event on [Form FDA 1932a](#), which is available online, within 15 business days; and
6. The labeling of the compounded drug includes all of the following:
 - name of drug;
 - strength of drug;
 - the species of the patient(s) and indication(s) for which the drug will be used;
 - the name, address, and contact information for the compounding pharmacy or compounding veterinarian;
 - the name, address, and contact information for the veterinarian ordering the office stock;
 - a beyond use date;
 - the statement, "Report suspected adverse reactions to the [pharmacist or veterinarian who compounded the drug] and to FDA using online [Form FDA 1932a](#)";
 - the statement, "This is a compounded drug. Not an FDA approved or indexed drug.";
 - the statement, "Not for use in food-producing animals"; and

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- the statement, “Caution: Federal law restricts this drug to use by or on the order of a licensed veterinarian.”³⁴

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

At this time, FDA generally does not intend to take enforcement action against the compounding of drugs from bulk drug substances 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 requirements for animal drug approval, adequate directions for use, and CGMP when all of the circumstances below are present:

1. The drug is compounded by or under the direct supervision of
 - a veterinarian, or
 - a pharmacist in a State-licensed pharmacy or a Federal facility;
2. The drug is compounded from a bulk drug substance on the “[List of Bulk Drug Substances for Compounding Drugs for Use in Food-Producing Animals or Free-Ranging Wildlife Species](#)”;
3. The prescribing veterinarian has a valid veterinarian-client-patient relationship 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 supply³⁵;
4. 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 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].”;
5. Upon becoming aware of any adverse event or product defect associated with a drug compounded from a bulk drug substance, the pharmacist or veterinarian who compounded the drug reports the event on [Form FDA 1932a](#), which is available online, within 15 business days; and
6. 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 compounding pharmacy or compounding veterinarian;

³⁴ 21 CFR 201.105(b)(1)

³⁵ Section 402(a) of the FD&C Act (21 U.S.C. § 342(a)); 21 CFR 530.20(b)(2)

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- the name, address, and contact information for the veterinarian ordering the antidote, or the wildlife health professional ordering the sedative or anesthetic;
- a beyond use date;
- prescribing veterinarian-determined withdrawal time;
- the statement, “Report suspected adverse reactions to the [pharmacist or veterinarian who compounded the drug] 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.”³⁶

IV. PAPERWORK REDUCTION ACT OF 1995

This guidance contains information collection provisions that are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. §§ 3501-3521). The time required to complete this information collection is estimated to average 1 minute per response, including the time to review instructions, search existing data sources, gather the data needed, and complete and review the information collection. Send comments regarding this burden estimate or suggestions for reducing this burden to:

Policy and Regulations Staff (HFV-6)
Center for Veterinary Medicine
Food and Drug Administration
7500 Standish Place, Rockville, MD 20855

An Agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. The OMB control number for this information collection is 0910-0904. To find the current expiration date, search for this OMB control number at <https://www.reginfo.gov>.

³⁶ 21 CFR 201.105(b)(1)

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APPENDIX

Request for Nominations to:

1. [The List of Bulk Drug Substances for Compounding Office Stock Drugs for Use in Nonfood-Producing Animals](#); or
2. [The List of Bulk Drug Substances for Compounding Drugs for Use in Food-Producing Animals or Free-Ranging Wildlife Species](#)

In a Federal Register notice published November 19, 2019, FDA established a public docket (FDA-2018-N-4626) so that interested parties could nominate bulk drug substances to a list of bulk drug substances for compounding office stock drugs for use in nonfood-producing animals or antidotes for food-producing animals (the List) and comment on nominated and evaluated bulk drug substances. In a *Federal Register* notice published April 8, 2022, FDA expanded nominations to include drugs compounded for use as sedatives or anesthetics for free-ranging wildlife species and also rearranged the List into two separate Lists as described above. This appendix incorporates information from the notices regarding the submission of nominations to these Lists.

Docket FDA-2018-N-4626 will remain open indefinitely to allow for nominations on a rolling basis.

Nominating a Bulk Drug Substance to a List:

When will FDA include a bulk drug substance on either of the Lists?

FDA intends to include a bulk drug substance on either of the Lists when:

1. There is no marketed FDA-approved, conditionally approved, or indexed animal drug(s) that can be used as labeled to treat the condition;
2. There is no marketed FDA-approved, conditionally approved, or indexed animal or human drug(s) with the same active ingredient(s) that could be used in an extralabel manner to treat the condition; and
3. FDA has not identified a significant safety concern specific to use of the bulk drug substance in animals.

For bulk drug substances used to compound drugs intended as office stock for nonfood-producing animals, in addition to 1- 3 above:

4. Urgent treatment with the compounded drug is necessary to avoid animal suffering or death, or to protect public safety.

For bulk drug substances used to compound drugs intended for use as antidotes in food-producing animals or for use as sedatives or anesthetics for free-ranging wildlife species, in addition to 1-3 above:

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5. There is sufficient scientific information for the prescribing veterinarian to determine appropriate withdrawal, withholding, or discard time(s) for meat, milk, eggs, or any food which might be derived from the treated animal(s).

How do I submit a nomination for one of the Lists?

You may submit nominations and comments to the docket through <https://www.regulations.gov>. The information to support nominations can be uploaded as attachments to your comment. The Docket No. is FDA-2018-N-4626.

You may submit written submissions to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All submissions must include the Docket No. FDA-2018-N-4626 for “Lists of Bulk Drug Substances for Compounding: Office Stock Drugs for Use in Nonfood-Producing Animals or Drugs for Use in Food-Producing Animals or Free-Ranging Wildlife Species.”

What information should I submit with the nomination?

You may nominate specific bulk drug substances for inclusion on either of the Lists. Each bulk drug substance should be submitted to the docket as its own, separate nomination. Submissions to the docket containing more than one bulk drug substance will not be considered an adequate nomination and will not be reviewed. Nominated substances that do not meet the definition of a bulk drug substance will not be evaluated for inclusion on a List.

For FDA to evaluate a bulk drug substance for inclusion on a List, you should submit the following information about the bulk drug substance and the compounded animal drug in the nomination:

1. Description of the Nominated Bulk Drug Substance:
 - (a) chemical name(s);
 - (b) common name(s);
2. Description of the Animal Drugs That Will be Compounded with the Nominated Bulk Drug Substance:
 - (a) dosage form(s) into which the nominated bulk drug substance will be compounded (e.g., capsule, tablet, suspension),
 - (b) strength(s) of the compounded drug(s), and
 - (c) intended route(s) of administration of the compounded drug(s) (e.g., oral, topical, injection, etc.).
3. Information Requested for FDA to Evaluate Nominated Bulk Drug Substances for Inclusion on a List:
 - (a) The species the drug to be compounded with the nominated bulk drug substance is intended to treat;

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- (b) The disease or condition(s) the drug to be compounded with the nominated bulk drug substance is intended to treat;
 - (c) If there is a marketed FDA-approved, conditionally approved, or indexed animal drug(s) that addresses the same condition(s) in the same species, an explanation of why a compounded drug is necessary (e.g., why the FDA-approved, conditionally approved, or indexed animal drug(s) is not suitable for a particular animal population);
 - (d) Confirmation that there is no marketed FDA-approved, conditionally approved, or indexed drug(s) that could be prescribed to treat the condition in the species that the drug compounded with the nominated substance is intended to address;
 - (e) If known by the nominator, if the nominated bulk drug substance is an active ingredient in a marketed FDA-approved, conditionally approved, or indexed animal or human drug(s), an explanation of why the animal drug cannot be compounded from the marketed FDA-approved, conditionally approved, or indexed animal or human drug;
 - (f) If known by the nominator, a description of any human user or animal safety concerns associated with use of the nominated bulk drug substance or finished compounded drug for the condition(s) in the species that the compounded drug is intended to address. If there are concerns, an explanation of why the concerns should not preclude inclusion of that nominated bulk drug substance on the List;
 - (g) For compounded drugs intended as office stock for nonfood-producing animals, an explanation of why the animal drug to be compounded with the nominated bulk drug substance is important to have available to the veterinarian for urgent treatment to avoid animal suffering or death, e.g., why animal suffering or death will result if treatment is delayed until a compounded animal drug can be obtained pursuant to a prescription for an individually identified animal; and
 - (h) For compounded drugs intended for use as antidotes to treat toxicoses in food-producing animals, or as sedatives or anesthetics for free-ranging wildlife species, relevant scientific literature or other evidence that demonstrates that the prescribing veterinarian has a basis for determining appropriate withdrawal, withholding, or discard time(s) for meat, milk, eggs, or any food which might be derived from the treated animal(s).
4. Contact information for FDA should there be follow-up questions regarding the nomination.

What about drugs that have been nominated for one of the Lists and are still under review?

FDA identifies those bulk drug substances that have been nominated and are under review at [Nominated Bulk Drug Substances Currently Under Review](#). At this time, FDA generally intends to refrain from taking enforcement action when these bulk drug substances currently under review are used to compound a finished drug as described in the nomination. Bulk drug substances will remain on [Nominated Bulk Drug Substances Currently Under Review](#) only during FDA's review of their nomination. If FDA completes its review and declines to place the bulk drug substance on a List based on the information provided, FDA will continue to accept and review any adequate

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additional information submitted by any party that supports the previously reviewed nomination. Should adequate additional information be provided such that FDA can conduct further substantial review, the bulk drug substance will again be placed on [Nominated Bulk Drug Substances Currently Under Review](#).

What happens when FDA approves or indexes a drug made with a bulk substance as described on one of the Lists?

FDA intends to remove a bulk substance from a List if a finished drug containing that substance in the appropriate dosage form and strength is approved or indexed. Please see [Bulk Drug Substances Reviewed and Not Listed](#).

What happens when FDA reviews a bulk drug substance and determines that it cannot be placed on a List because of insufficient information or because of other reasons (e.g., safety concerns)?

Please see [Bulk Drug Substances Reviewed and Not Listed](#) for those bulk drug substances that have been reviewed by FDA but are not on either List.