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Compounding Animal Drugs from Bulk Drug Substances

Guidance for Industry

Draft Guidance

This guidance document is for comment purposes only.

Submit comments on this draft guidance by the date provided in the *Federal Register* notice announcing the availability of the draft guidance.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 (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number FDA-2018-D-4533.

For questions regarding this document, contact Eric Nelson (CVM) at 240-402-7001, or by e-mail at cvmcompliance@fda.hhs.gov.

Additional copies of this draft guidance document may be requested from the Policy and Regulations Staff (HFV-6), Center for Veterinary Medicine, Food and Drug Administration, 7500 Standish Place,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 either https://www.fda.gov/animal-veterinary or https://www.regulations.gov/.

U.S. Department of Health and Human Services
Food and Drug Administration
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This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA or Agency) current thinking on this topic.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) policy regarding the compounding of animal drugs from bulk drug substances[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]

Under the Federal Food, Drug, and Cosmetic Act (FD&C Act), 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, conditional approval, or indexing requirements (sections 512, 571, and 572 of the FD&C Act (21 U.S.C. §§ 360b, 360ccc, 360ccc-1)). Further, all animal drugs are required to, among other things, be made in accordance with current good manufacturing practice (cGMP) requirements

[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. In addition, for purposes of this guidance, FDA considers bulk chemicals used to make antidotes intended to treat toxicoses in animals to be bulk drug substances.

[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 or regulations governing their practice.

(section 501(a)(2)(B)) of the FD&C Act (21 U.S.C. § 351(a)(2)(B)) and 21 CFR parts 210 and 211) and have adequate directions for use (section 502(f)(1) of the FD&C Act (21 U.S.C. § 352(f)(1)). However, FDA has generally exercised enforcement discretion with regard to animal drug compounding from bulk drug substances under certain circumstances when no other medically appropriate treatment options exist. This guidance, a continuation of this practice, is intended to provide additional information and clarity to veterinarians and pharmacists about FDA's current thinking with respect to 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 does not intend to take enforcement action for violations of the FD&C Act's requirements for approval, adequate directions for use, and cGMP requirements, for these products that meet the circumstances described below. The policies described in this document aim to protect human and animal health by limiting the use of animal drugs compounded from bulk drug substances primarily to situations in which a veterinarian is acting within a valid veterinarian-client-patient relationship (VCPR) [3] and there is no medically appropriate drug that is FDA-approved, conditionally approved, or on the Index of Legally Marketed Unapproved New Animal Drugs for Minor Species (indexed) to treat the animal. These policies are also intended to address FDA's concerns with compounding animal drugs from bulk drug substances, including significant concerns with such drugs when they:

- present particular human or animal safety concerns;
- are intended for use in food-producing animals[4];
- are copies of marketed FDA-approved, conditionally approved, or indexed drugs[5]; or
- are compounded without a patient-specific prescription (*i.e.*, office stock).

This guidance does not apply to animal drugs compounded for use in investigations of new animal drugs (21 CFR part 511) or to animal drugs compounded from marketed FDA-approved animal or human drugs, which are considered extralabel uses of such drugs. Compounding animal drugs from approved drugs is lawful if the requirements for extralabel use under the FD&C Act and FDA regulations are met (sections 512(a)(4) and (5) of the FD&C Act and 21 CFR part 530).

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[3] 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 Title 21 of the Code of Federal Regulations (21 CFR) section 530.3(i).

[4] 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.

[5] For purposes of this guidance, an FDA-approved, conditionally approved, or indexed animal drug or FDA-approved human drug is "marketed" if the drug manufacturer is making and offering the drug for sale. In addition, an FDA-approved human drug is not "marketed" if it is on the drug shortage list in effect under section 506E of the FD&C Act.

Additionally, this guidance does not address pharmacist, pharmacy, and veterinarian responsibilities under the Controlled Substances Act (21 U.S.C. §801, et. seq.) or applicable State laws.

In general, FDA's guidance documents 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 guidance documents means that something is suggested or recommended, but not required.

II. BACKGROUND

A. Legal Marketing Pathways for Animal Drugs

To be legally marketed, animal drugs, with few exceptions, must be approved by FDA under section 512 of the FD&C Act, conditionally approved by FDA under section 571 of the FD&C Act, or indexed under section 572 of the FD&C Act.[6]

A drug company seeking FDA approval of an animal drug application ("applicant" or "sponsor") 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. In addition to other approval requirements, sponsors who seek FDA approval of a drug for use in food-producing animals must submit data regarding the drug's potential for creating harmful residues in the meat, milk, eggs, and other edible products from treated animals. Based on these data, FDA may approve the drug with residue tolerances; withdrawal, withholding, and/or discard times; and other conditions of use to prevent products from treated animals that contain harmful residues from entering the food supply.

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 adverse event reports, including reports of product defects, and provide information to the FDA related to safety, effectiveness, and manufacturing quality throughout the lifetime of the product. These reports allow FDA to continue to monitor the safety and effectiveness of the drug after approval.

[6] 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.

The conditional approval[7] and indexing[8] processes provide alternative pathways to legal marketing that address the specific challenges associated with full FDA approval for drugs intended for minor uses,[9] minor species,[10] or for certain other new animal drugs. Like the approval process under section 512, these provisions protect human and animal health by requiring FDA review of data regarding safety and effectiveness 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 FD&C Act does not generally distinguish between compounding animal drugs from bulk drug substances and other methods of animal drug manufacturing.[11] 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.

Animal drugs compounded from bulk drug substances are not FDA-approved brand-name (*i.e.*, pioneer) drugs, nor are they FDA-approved generic drugs. As a result, animal drugs compounded from bulk drug substances have not been reviewed by FDA for evidence that they are safe, effective, properly manufactured, and accurately labeled. Further, when the compounded drug is for a food-producing animal, FDA has not reviewed evidence supporting conditions of use to protect against harmful drug residues. Finally, unlike sponsors of approved animal drugs, compounders are not required to report to FDA adverse events and product defects regarding animal drugs compounded from bulk drug substances.

The law permits compounding of animal drugs when the source of the active ingredient is a finished FDA-approved drug, and not a bulk drug substance. Specifically, the extralabel use

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[7] "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.

[8] "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.

[9] 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)).

[10] The term "minor species" means animals other than humans that are not major species. Section 201 (oo) of the FD&C Act. Major species are dogs, cats, horses, pigs, cattle, turkeys, and chickens. Section 201 (nn) of the FD&C Act.

[11] 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.

provisions of the FD&C Act (section 512(a) (4) and (5)) 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 the implementing regulations at 21 CFR part 530 are met. These regulations state that, "[n]othing in this part shall be construed as permitting compounding from bulk drugs." 21 CFR 530.13(a).

Although numerous drugs are FDA-approved, conditionally 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, conditionally 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, conditionally 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.

III. POLICY

In developing this guidance, FDA has attempted to balance its 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, conditionally approved, or indexed drug can be used to treat the animal. Because of the safety benefits and protections of the pre-market review process and post-market monitoring of FDA-approved, conditionally approved, and indexed drugs, veterinarians should only use drugs compounded from bulk drug substances if FDA-approved, conditionally approved, or indexed drugs are not available to treat the animal. At this time and based on our current understanding of the risks of compounding animal drugs from bulk drug substances, FDA does not intend to take enforcement action for violations of the FD&C Act's requirements for approval, adequate directions for use, and cGMP requirements, for these products that meet the circumstances described below.

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 human or animal safety concerns. Some examples include superpotency leading to animal overdose, microbial contamination, and drug formulations that present safety risks for the treated animals or for people handling or administering the animal drug.
- 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 to be present in food from treated animals. However, FDA recognizes that in some cases of toxicosis in food-producing animals, which can be life-threatening and affect large groups of animals that are all exposed to the same known toxin in their shared environment, an antidote compounded from a bulk drug substance may be the only treatment option and may be needed immediately to prevent animal suffering or

death. As described below, this guidance describes circumstances in which, at this time and based on our current understanding of the risks of animal drugs compounded from bulk drug substances, FDA does not intend to take enforcement action for limited compounding of certain antidotes for food-producing animals. In these cases, we expect the prescribing veterinarian, acting within a valid VCPR, to establish appropriate, scientifically supportable withdrawal, withholding, and discard times[12] to ensure that animals treated with antidotes do not contain residues of the antidotes or the toxin,[13] or alternatively, to ensure that the treated animals do not enter the food supply.

- Are copies of a marketed FDA-approved, conditionally approved, or indexed drug. 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.
- Are sold as office stock (as opposed to dispensed by a pharmacy upon receipt of a prescription[14] for an identified patient[15]). The Agency is concerned that compounded office stock potentially exposes larger numbers of animals to drugs of unproven safety, effectiveness, and manufacturing quality. However, FDA recognizes that in some cases an animal drug is needed immediately, and the time needed to compound a drug in response to an individual patient prescription may result in animal suffering or death. As described below, this guidance explains circumstances under which at this time and based on our current understanding of the risks of animal drugs compounded from bulk drug substances, FDA does not intend to take enforcement action for limited compounding of office stock.

Consistent with these concerns, FDA has developed this draft guidance to explain when the Agency, at this time and based on our current understanding of the risks of animal drugs compounded from bulk drug substances, does not intend to take enforcement action for violations of the FD&C Act's requirements for approval; adequate directions for use; and cGMP requirements. When pharmacies and veterinarians compound animal drugs from bulk substances as described below, FDA intends to generally defer to their State licensing boards for day-to-day

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[12] Sources of appropriate scientific information for setting withdrawal, withholding, and discard times could include, for example, relevant scientific literature or other evidence submitted by the person nominating the bulk drug substance to the List of Bulk Drug Substances for Use in Compounding Office Stock Drugs for Use in Nonfood-Producing Animals or Antidotes for Food-Producing Animals, information from the Food Animal Residue Avoidance & Depletion Program (FARAD) (www.farad.org), published textbooks, and peer-reviewed published journal articles.

[13] Food containing residues of the antidote or the toxin the antidote is intended to treat may be considered adulterated under section 402(a) of the FD&C Act (21 U.S.C. § 342(a)).

[14] 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.

[15] For purposes of this guidance, 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).

oversight. Nonetheless, the Agency may take action when animal drugs compounded from bulk drug substances (1) present particular human or animal safety concerns or, (2) 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). Regardless of whether FDA intends to take action, FDA may refer a case to the appropriate state entity.

A. Compounding Pursuant to Patient-Specific Prescriptions for Nonfood-Producing Animals

At this time and based on our current understanding of the risks of animal drugs compounded from bulk drug substances, FDA 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 new animal drug approval requirements in sections 512 and 501(a)(5) of the FD&C Act, the adequate directions for use requirements in section 502(f)(1) of the FD&C Act, and the cGMP requirements in section 501(a)(2)(B) of the FD&C Act, provided:

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 accordance with the current United States Pharmacopeia and National Formulary (USP-NF) Chapters <795> "Pharmaceutical Compounding – Nonsterile Preparations" or <797> "Pharmaceutical Compounding-Sterile Preparations" and complies with the standards of all applicable USP-NF monographs (*e.g.*, a monograph for a bulk drug substance or a monograph for a compounded finished product);
3. 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 and is not dispensed or transferred to a third party (*e.g.*, distributor, retailer, veterinarian who did not write the prescription); 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;
4. The compounded drug is not a copy of a marketed FDA-approved, conditionally approved, or indexed animal drug or an FDA-approved human drug. For purposes of this guidance, a drug compounded from bulk drug substance is a copy if it has
    (a) the same active ingredient as a marketed FDA-approved, conditionally approved, or indexed animal drug or an FDA-approved human drug, and
    (b) can be given by the same route of administration as the marketed FDA-approved, conditionally approved, or indexed animal drug or FDA-approved human drug, and

(c) is in the same, similar, or easily substitutable strength[16] as the marketed FDA-approved, conditionally approved, or indexed animal drug or FDA-approved human drug,

provided that there is not a difference between the compounded drug and the FDA-approved, conditionally approved, or indexed animal drug or FDA-approved human drug that will produce a clinical difference in the identified patient, and the medical rationale is documented in the prescription, or if a veterinarian is compounding the drug, the medical rationale is noted in the patient's medical record. For example, the patient requires a 1.0% solution and the FDA-approved solution is 0.1%;

5. If the compounded drug contains the same active moiety[17] as a marketed FDA-approved, conditionally approved, or indexed animal drug or an FDA-approved human drug but as a different salt, ester, or other noncovalent derivative, there is a difference between the compounded drug and the marketed FDA-approved, conditionally approved, or indexed animal drug or FDA-approved human drug that will produce a clinical difference in the identified patient, and the medical rationale is documented in the prescription, or if a veterinarian is compounding the drug, the medical rationale is noted in the patient's medical record;

6. If the compounded animal drug has any of the same active ingredient moiety(ies) as one or more marketed FDA-approved, conditionally approved, or indexed animal drugs or FDA-approved human drugs, the compounder has determined and documented the reason(s) why the FDA-approved, conditionally approved, or indexed animal drug(s) or FDA-approved human drug(s) cannot be used as the source of the active ingredient(s).[18] One reason may be that the chemical properties of the FDA-approved, conditionally approved, or indexed animal drug or FDA-approved human drug prevent its practical and effective use in compounding. For example, it may not be possible to compound an ophthalmic solution from an approved topical cream;

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[16] An easily substitutable strength is one where the same or similar dosage can be achieved by administration of fractional or multiple doses of a drug product.

[17] 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.

[18] While the FD&C Act prohibits the extralabel use of conditionally approved and indexed animal drugs, under this guidance, at this time and based on our current understanding of the risks of animal drugs compounded from bulk drug substances, FDA 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.

7. Upon becoming aware of any adverse event[19] or product defect[20] associated with an animal drug compounded from a bulk drug substance, the pharmacy or veterinarian that compounded the drug reports the event on Form FDA 1932a, which is available online, within 15 days; and
8. The labeling of the compounded drug includes the following, in addition to any other information required by State law:
    - name of drug;
    - strength of drug;
    - identifying information about the patient including the species of the patient, 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 adverse events to FDA using online Form FDA 1932a";
    - the statement, "This is a compounded drug"; and
    - the statement, "Caution: Federal law restricts this drug to use by or on the order of a licensed veterinarian."

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

At this time and based on our current understanding of the risks of animal drugs compounded from bulk drug substances, FDA 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 violations of the new animal drug approval requirements in sections 512 and 501(a)(5) of the FD&C Act, the adequate directions for use requirements in section 502(f)(1) of the FD&C Act, and the cGMP requirements in section 501(a)(2)(B) of the FD&C Act, provided:

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

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

[20] 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.

Office Stock Drugs for Use in Nonfood-Producing Animals or Antidotes for Food-Producing Animals" (https://www.fda.gov/animal-veterinary/animal-drug-compounding/list-bulk-drug-substances-compounding-office-stock-drugs-use-nonfood-producing-animals-or-antidotes) described in the appendix to this guidance;

3. The drug is compounded in accordance with the current United States Pharmacopeia and National Formulary (USP-NF) Chapters <795> "Pharmaceutical Compounding – Nonsterile Preparations" or <797> "Pharmaceutical Compounding-Sterile Preparations" and complies with the standards of all applicable USP-NF monograph (*e.g.*, a monograph for a bulk drug substance or a monograph for a compounded finished product);
4. Except for a veterinarian dispensing the drug to the owner or caretaker of his or her animal patient or to another veterinarian in the same practice located in the same physical location, the drug is not dispensed or transferred by the pharmacy, pharmacist, or veterinarian to a third party (*e.g.*, distributor, retailer, or veterinarian in another practice);
5. Upon becoming aware of any adverse event or product defect associated with an animal drug compounded from a bulk drug substance, the pharmacy or veterinarian that compounded the drug reports the event on Form FDA 1932a, which is available online, within 15 days; and
6. The labeling of the compounded drug includes 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 adverse events to FDA using online Form FDA 1932a";
    - the statement, "This is a compounded drug";
    - 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."

C. Compounding Drugs for Use as Antidotes for Food-Producing Animals

At this time and based on our current understanding of the risks of animal drugs compounded from bulk drug substances, FDA 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 for violations of the new animal drug approval requirements in sections 512 and 501(a)(5) of the FD&C Act, the adequate directions for use requirements in section 502(f)(1) of the FD&C Act, and the current good manufacturing practices requirements in section 501(a)(2)(B) of the FD&C Act, provided:

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 Office Stock Drugs for Use in Nonfood-Producing Animals or Antidotes for Food-Producing Animals" (https://www.fda.gov/animal-veterinary/animal-drug-compounding/list-bulk-drug-substances-compounding-office-stock-drugs-use-nonfood-producing-animals-or-antidotes);
3. The veterinarian establishes and documents a scientifically based withdrawal time that ensures residues of the antidote and the underlying toxin are not present in the animal at the time of slaughter or the veterinarian ensures the animal does not enter the food supply;
4. Upon becoming aware of any adverse event or product defect associated with a drug compounded from a bulk drug substance, the pharmacy or veterinarian that compounded the drug reports the event on Form FDA 1932a, which is available online, within 15 days; and
5. The labeling of the antidote includes all 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;
    - the name, address, and contact information for the veterinarian ordering the antidote;
    - a beyond use date;
    - veterinarian-determined withdrawal time;
    - the statement, "Report adverse events to FDA using online Form FDA 1932a";
    - the statement, "This is a compounded drug"; and
    - the statement, "Caution: Federal law restricts this drug to use by or on the order of a licensed veterinarian."

APPENDIX

Request for Nominations to the List of Bulk Drug Substances for Compounding:

1. **Office Stock Drugs for Use in Nonfood-Producing Animals**

2. **Antidotes for Food-Producing Animals**

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. This appendix provides information from the notice regarding the submission of nominations.

When Will FDA Include a Bulk Drug Substance on the List of Bulk Drug Substances for Compounding Office Stock Drugs for Use in Nonfood-Producing Animals or Antidotes for Food-Producing Animals?

FDA intends to include a bulk drug substance on the List (https://www.fda.gov/animal-veterinary/animal-drug-compounding/list-bulk-drug-substances-compounding-office-stock-drugs-use-nonfood-producing-animals-or-antidotes) when:

1. There is no marketed FDA-approved, conditionally approved, or indexed animal drug that can be used as labeled to treat the condition;
2. There is no marketed FDA-approved animal or human drug that could be used in an extralabel manner under section 512(a)(4) or (a)(5) of the FD&C Act and 21 CFR part 530 to treat the condition;
3. The drug cannot be compounded from a marketed FDA-approved animal or human drug consistent with 21 CFR part 530;
4. Immediate treatment with the compounded drug is necessary to avoid animal suffering or death; and
5. 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 for use as antidotes in food-producing animals, in addition to 1-5 above:

6. There is sufficient scientific information for the 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 the List?

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 "List of Bulk Drug Substances for Compounding Office Stock Drugs for Use in Nonfood-Producing Animals or Antidotes for Food-Producing Animals."

What information should I submit with the nomination?

You may nominate specific bulk drug substances for inclusion on the List. 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. In addition, nominations will only be evaluated if they are for specific active ingredients that meet the definition of a bulk drug substance. Nominated substances that do not meet this definition will not be evaluated for inclusion on the List.

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

1. **Confirmation That the Nominated Substance is a Bulk Drug Substance:**

   A statement that the nominated substance meets the definition of bulk drug substance.

2. **Description of the Nominated Bulk Drug Substance:**

   (a) chemical name(s);

   (b) common name(s);

   (c) chemical grade (*e.g.*, USP-NF, ACS, etc.);

   (d) description of the strength, stability, purity; and

   (e) how the nominated bulk drug substance is supplied (*e.g.*, powder, liquid).

3. **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).

4. Information Requested for FDA to Evaluate Nominated Bulk Drug Substances for Inclusion on the List:

(a) The species and condition(s) that the drug to be compounded with the nominated bulk drug substance is intended to treat;

(b) A bibliography of scientific literature containing safety and effectiveness data for the drug compounded using the nominated bulk drug substance;

(c) A list of animal drugs, if any, that are FDA-approved, conditionally approved, or indexed for the condition(s) in the species that the drug compounded with the nominated bulk drug substance is intended to address;

(d) If there are marketed FDA-approved, conditionally approved, or indexed drugs that address the same condition(s) in the same species, an explanation, supported by relevant scientific literature or other evidence, of why a compounded drug is necessary (*e.g.*, why the FDA-approved drug is not suitable for a particular animal population);

(e) Confirmation, using supporting evidence, that there are no marketed FDA-approved animal or human drugs that could be prescribed in an extralabel manner under section 512(a)(4) and (a)(5) of the FD&C Act and 21 CFR part 530 to treat the condition(s) in the species that the drug compounded with the nominated bulk drug substance is intended to address;

(f) If the nominated bulk drug substance is an active ingredient in a marketed FDA-approved animal or human drug, an explanation, supported by appropriate scientific data or information, of why the animal drug cannot be compounded from the marketed FDA-approved animal or human drug under 21 CFR 530.13(b);

(g) An explanation, supported by relevant scientific literature or other evidence, of why the animal drug to be compounded with the nominated bulk drug substance must be available to the veterinarian for immediate treatment to avoid animal suffering or death. Nominations should include specific information documenting that 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) 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, supported by scientific literature or other evidence, of why the concerns should not preclude inclusion of that nominated bulk drug substance on the List.

(i) For compounded drugs intended for use as antidotes to treat toxicoses in food-producing animals, 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).