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Alliance for Pharmacy Compounding

November 16, 2021

Dr. Steven Solomon, DVM, Director
Center for Veterinary Medicine
U.S. Food and Drug Administration
7500 Standish Pl, HFV-1
Rockville, MD 20855

Dear Dr. Solomon:

I write on behalf of the Alliance for Pharmacy Compounding to offer a substantive alternative to CVM's GFI #256 that we believe attends to concerns your agency seeks to address via the GFI while not interfering with the practice of veterinary medicine or impeding access to compounded preparations for animal patients.

As you may know, APC is the voice for pharmacy compounding, representing compounding pharmacists and technicians in both 503A and 503B settings, as well as prescribers, educators, researchers, and suppliers. Pharmacists' ability to compound medications from pure ingredients is authorized in federal law and for good reason: Manufactured drugs don't come in strengths and dosage forms that are right for everyone, and prescribers need to be able to prescribe customized medications when, in their judgment, a manufactured drug is not the best course of therapy for a human or animal patient. Every day, APC members play a critical role in patients' lives, preparing essential, custom medications for a range of health conditions, including autism, oncology, dermatology, ophthalmology, pediatrics, women's health, animal health, and others.

Although APC submitted comments on GFI #256 in October 2020, we have continued to contemplate the matter. The result of that contemplation is the accompanying proposal – a marked up version of CVM's proposed GFI that we believe will address your agency's concerns while not impeding timely access to critically needed medications for animals.

This proposal reflects the input of a wide range of stakeholders, including compounding pharmacists, veterinarians, veterinary medical associations, pharmacy organizations, animal shelters, boards of pharmacy, pet owners and others. While we disagree that the FDA has clear authority to adopt guidance of this sort, we believe that a reasonable meeting of the minds on a workable GFI can avoid costly litigation that may result from a GFI that interferes with veterinary medical judgment and practice.

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The accompanying markup makes largely modest amendments to your original GFI 256, protects the animals that we provide necessary care for, is acceptable to APC, and is likely to be acceptable to other animal compounding stakeholders.

We support the development of a meaningful adverse event reporting system that requires disclosure of significant and serious adverse events. We believe that any adverse event reporting *must* include direct contact with the pharmacy so that personnel there may immediately address any safety concerns and determine the severity of the event. The adverse event reporting system should not be overly burdensome on veterinarians who already have significant time constraints on their ability to practice medicine. We are hopeful that comprehensive safety information will allow regulations and guidance that are based upon data and not on vague and undocumented safety concerns. We do not believe that the current FDA Form 1932a is adequate for these purposes.

We also support clear rules on what constitutes an "Essentially a Copy" of FDA approved drugs. Regarding Essential Copy rules, our proposal is an adaptation of FDA's guidance for 503A pharmacies that make human health drugs. We've tailored it to allow for changes in strength, dosage form, ingredients, and flavors that are necessary and critical for animal patients. We believe that these rules will support FDA's NDA process and give manufacturers comfort that the medications they take through the approval process will receive appropriate exclusivity and will not be copied.

Please note that we moved the provisions regarding ordering drugs for office stock to section A of the mark-up. We believe strongly that veterinarians should be free to treat patients as they determine in their medical judgment is appropriate, and this includes the ability to stock small quantities of drugs in their offices for emergency and urgent uses. Office stock is not a safety issue. Rules regarding ordering drugs for office stock have been established by many states and vary widely. We believe that this is a matter best determined by local practices and interests. Some have argued that large scale ordering of drugs for office stock makes this more akin to drug manufacturing. Our members' experience shows that office stock orders are typically small and only cover those drugs that are necessary to have on hand for urgent need.

Lastly, APC and its members urge:

1. That the next version of GFI #256 remain a draft. FDA has received a significant amount of stakeholder feedback on the concerns of this GFI, and those stakeholders need another opportunity to review and provide feedback before any guidance is finalized.
2. That APC and veterinary medical associations be allowed to advise the FDA in developing final guidance.
3. That FDA CVM permit no less than two years for implementation of any new guidance. Although it's not a law or regulation, we anticipate that state boards of pharmacy, the regulators of state-licensed pharmacies, will likely respond to your GFI by creating harmonious regulation. Time will be required to consider and do so properly. In addition, changes to the way veterinarians and pharmacies work together to serve patients could change drastically as a result of a final guidance, and ample time for implementation is required to ensure that the continuity of patient care is not interrupted.

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Thank you for giving attention to the accompanying markup. We sincerely welcome the possibility of working together on this GFI and to implementing guidance that is both rigorous and practical in protecting medication access and the health of animal patients.

Sincerely,

Scott Brunner, CAE
Chief Executive Officer
scott@a4pc.org

c: APC Board of Directors

#256

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 (HFA305), 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
Center for Veterinary Medicine
November 2019

Contains Nonbinding Recommendations
Draft – Not for Implementation

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Compounding Animal Drugs from Bulk Drug Substances

Guidance for Industry

Commented [BS1]: We do not agree with the legal premise upon which FDA proposes to regulate animal health compounding or the policy reasons why FDA believes such regulation is necessary. Notwithstanding our position on these issues, we have generally refrained from commenting on these sections of draft GFI #256. In some instances, however, we have left in changes or comments where we believe these changes are necessary to conform with the substantive proposals elsewhere in the document. Instead of commenting on the authority and policy issues, we have focused our attention and energies on proposing workable solutions to the issues presented that address the needs of all stakeholders.

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:

[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

- 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 (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, drugs that have been FDA approved, conditionally approved or indexed do not always meet all of the requirements and standards of care in veterinary medicine due to frequent manufacturer backorders, variability in size, and challenges with medication administration. In addition, animal health compounding has traditionally been regulated by State Boards of Pharmacy. Therefore, FDA has generally exercised enforcement discretion with regard to animal drug compounding from bulk drug substances under certain circumstances when a veterinarian determines that 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 where the veterinarian, in their sole medical judgement,

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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.

[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

determines that 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]; or
- are Essentially a Copy of Commercially Available marketed FDA-approved, conditionally approved, or indexed drugs as provided in the rules attached as Exhibit A; ~~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).

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.

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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.

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.[5]

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.

The conditional approval[6] and indexing[7] processes provide alternative pathways to legal marketing that address the specific challenges associated with full FDA approval for drugs

Commented [BS2]: As noted above, while we strongly disagree with the position set forth in Sections II A and B and III below, we are not commenting on any specific points made.

[5] 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.

[6] "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.

[7] "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.

intended for minor uses,[8] minor species,[9] 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.[10] 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 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

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[8] 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)).

[9] 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.

[10] 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.

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 is available 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 when (i) such drugs are not "Commercially Available" , (ii) the veterinarian, in their sole medical judgement, determines that no such drug is appropriate to treat their patient or (iii) a pharmacist determines, in their professional judgment, that there is a clinical reason why such approved, conditionally approved or indexed drug is not appropriate to use as the basis of a compounded medication. Examples of such clinical reasons include: such drug includes unnecessary excipients or likely allergens or is in a strength or dosage form that makes compliance unnecessarily difficult or unlikely. 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[11] to ensure that animals treated with antidotes do not contain residues of the antidotes or the toxin,[12] or alternatively, to ensure that the treated animals do not enter the food supply.

- Are "Essentially a Copy" of a Commercially Available 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[13] for an identified patient[14]). 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 oversight. ~~Nonetheless, the Agency may take action when animal drugs compounded from bulk~~

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[11] 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.

[12] 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)).

~~[13] 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.~~

[14] 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).

~~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 a Veterinarian's Order for Office Use or 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 pharmacy, after the receipt of an order from a veterinarian to the veterinarian's office, where administration or further specific patient dispensing within a valid VCPR may occur, or to another veterinarian in his or her practice located in the same physical location;
   (c) 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 drugs are not Essentially Copies of a Commercially Available marketed FDA-approved, conditionally approved, or indexed animal drug or an FDA-approved human drug provided that the veterinarian has determined that there is a clinical or compliance difference for their patient. See Exhibit A. Two examples: ~~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~~

Commented [BS3]: Species that are sometimes eaten, but also kept under conditions that preclude their routine use as food, or animals that belong to the early non-food life stage of a food-producing minor species where that life stage is not eaten, shall be defined as nonfood-producing animals.

Deleted: For purposes of this guidance, a drug compounded from bulk drug substance is a copy if it has ¶ the same active ingredient as a marketed FDA-approved, conditionally approved, or indexed animal drug or an FDA-approved human drug, and ¶ 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 ¶

~~the patient's medical record. For example,~~ the patient requires a 1.0% solution and the FDA-approved solution is 0.1%; the patient is a fractious cat who is unwilling to take an available pill, but willingly takes a soft chew or flavored suspension of medication. The pharmacy order and/or prescription for the medication is sufficient medical rationale, as is the documentation in the patient's medical record for medication compounded by the veterinarian.

5. ~~If the compounded drug contains the same active moiety[15] 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;~~

   5. If the compounded animal drug has any of the same active ingredient moiety(ies) as one or more Commercially Available 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). [16] 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; Other examples include toxicity, allergies or other sensitivities to excipients, hard coatings, strength variability and available dosage forms do not translate to other dosage forms.

6. Upon becoming aware of any Unexpected, Serious Adverse Drug Experience or Product Defect as defined on Exhibit B 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 30 ~~15~~ days; and

Commented [MB4]: While fractional or multiple doses of a medication may be adaptable for human consumption, they make medication accuracy and administration very difficult if not impossible in an animal context. Some human health generic tablets would have to be fractionated into 6 equal pieces—opening the dosing up to extreme variability and bitterness. The same goes for multiple doses. You may be able to hide a pill in a piece of cheese for a large dog, but they figure out how to spit out that one pill, let alone attempting to administer multiples. Compounding offers an alternative where our very small patients and very large patients have an opportunity for accurate and compliance friendly dosing.

[15] 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.

[16] 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. The labeling of patient-specific compounded drugs will be in accordance with State laws. The labeling of non patient-specific office use compounded drugs includes the following, in addition to any other information required by State law:

    - name of drug;
    - strength of drug;
    - ~~for patient-specific prescriptions, 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);~~
    - ~~for patient-specific prescriptions, the name, address, and contact information for the compounding pharmacy or veterinarian and name of prescribing veterinarian;~~
    - a beyond use date;
    - the statement, "To report serious adverse events call" followed by a phone number to the compounding facility;~~to FDA using online Form FDA 1932a~~";
    - the statement, "This is a compounded drug"; and
    - 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."
    - Additional prescription labeling requirements per the state where the veterinarian and the pharmacy operate

B. ~~Compounding Without Patient-Specific Prescriptions ("Office Stock") for NonfoodProducing 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 nonfoodproducing 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 Office Stock Drugs for Use in Nonfood-Producing Animals or Antidotes for FoodProducing Animals" (https://www.fda.gov/animal-veterinary/animal-drugcompounding/list-bulk-drug-substances-compounding-office-stock-drugs-use-nonfoodproducing-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 Antidotes for Food-Producing Animals" (https://www.fda.gov/animalveterinary/animal-drug-compounding/list-bulk-drug-substances-compounding-officestock-drugs-use-nonfood-producing-animals-or-antidotes);
3. The veterinarian specifies 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 30 ~~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, "To report serious adverse events call" followed by a phone number to the compounding facility; ~~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~~ as 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/animalveterinary/animal-drug-compounding/list-bulk-drug-substances-compounding-office-stock-drugsuse-nonfood-producing-animals-or-antidotes) when:

1. There is no Commercially Available marketed FDA-approved, conditionally approved, or indexed animal drug that can be used as labeled to treat the condition;
2. There is no Commercially Available 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 Commercially Available 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 Commercially Available 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 Commercially Available 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 Commercially Available 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 foodproducing 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).

Exhibit A

A. **Commercially Available Drug Product**

A drug product is Commercially Available if it is an FDA-approved, marketed drug product. A drug product is not Commercially Available if

- the drug product has been discontinued and is no longer marketed[17];
- the drug product appears on the FDA drug shortage list in effect under section 506E of the FD&C Act.[18] A drug "appears on the drug shortage list in effect under section 506E" if the drug is in "currently in shortage" status (and not in "resolved" status) in FDA's drug shortage database; or
- the drug product is not available to veterinarians or pharmacies through wholesale distribution channels or otherwise without undue restriction and in amounts necessary to meet supply needs; the drug product is on allocation or back order and excludes veterinarians and/or pharmacies; or the manufacturer of the drug product prohibits distribution of the drug product to veterinarians and/or pharmacies.

B. **Essentially a Copy of a Commercially Available Drug Product**

1. *What is Essentially a Copy?*

FDA intends to consider a compounded drug product to be Essentially a Copy of a Commercially Available drug product if:

- the compounded drug product has the same active pharmaceutical ingredient(s) (API) as the Commercially Available drug product;
- the dosage strength of the compounded drug is the same or similar (as defined below) to the dosage strength of the Commercially Available drug product; and
- the Commercially Available drug product is the same dosage form as prescribed for the compounded drug, unless a prescriber determines that there is a change required which produces, for that patient or patient population, a significant difference from the commercially available drug product, which determination shall be deemed to exist if a veterinarian prescribes or orders such compounded drug product.

[17] FDA maintains a list of approved drug products that sponsors have indicated are not marketed in the discontinued section of the list of Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book). See http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm. Specifically, the list includes approved drug products that have never been marketed, are for exportation, are for military use, have been discontinued from marketing and we have not determined were withdrawn for safety or effectiveness reasons, or have had their approvals withdrawn for reasons other than safety or effectiveness subsequent to being discontinued from marketing.

[18] See http://www.accessdata.fda.gov/scripts/drugshortages/default.cfm.

a. Same API

With regard to the characteristics listed above, an API is the substance in a drug product 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 function of the body. When a compounded drug product offers the same API as a Commercially Available drug product, in the same or a similar dosage strength within 10% of the Commercially Available drug product and in the same dosage form as the Commercially Available drug product, we generally intend to consider such a drug product Essentially a Copy, unless a prescriber determines that there is a change, that will produce a significant difference for that patient. We recognize that, for some patients, a drug product that has the same API, strength, and dosage form may include a change that produces a significant difference for a particular patient. For example, a drug product compounded without a particular inactive ingredient may produce a significant difference for a patient who has an allergy to the inactive ingredient in the commercially available drug product. However, for other patients, this change may produce no difference at all. In the context of compounding, we generally intend to consider such a drug Essentially a Copy unless a prescriber determines that there is a change that will produce a significant difference for the patient for whom it is prescribed. A valid prescription or order provided by a veterinarian will be deemed to be a determination that a significant difference exists.

b. Same or Similar Strength [19]

FDA generally intends to consider two drugs to have a similar dosage strength if the dosage strength of the compounded drug is within 10% of the dosage strength of the Commercially Available drug product and strengths beyond 10% shall not be considered similar.

c. Same Dosage Form

Dosage form is the method for delivering a drug to a patient (e.g., tablet, capsule, oral liquid, injectable liquid, topical cream).In general, FDA does not intend to consider a compounded drug product with the same API and the same or similar strength to be Essentially a Copy of a Commercially Available drug product if the compounded drug product and the Commercially Available drug product have different dosage forms (e.g., if the Commercially Available drug product is an oral tablet and the compounded drug product is an oral liquid). However, if the compounded drug product has the same API and the same or similar strength as the Commercially Available drug product and the Commercially Available drug product is a dosage form that can be administered to the patient in the same manner prescribed for the compounded drug (e.g., if the

[19] Note- we removed the concept of easily substitutable strength as this does not work for animal patients. While fractional or multiple doses of a medication may be adaptable for human consumption, they make medication accuracy and administration very difficult if not impossible in an animal context. Some human health generic tablets would have to be fractionated into 6 equal pieces—opening the dosing up to extreme variability and bitterness. The same goes for multiple doses. You may be able to hide a pill in a piece of cheese for a large dog, but they figure out how to spit out that one pill, let alone attempting to administer multiples. Compounding offers an alternative where our very small patients and very large patients have an opportunity for accurate and compliance friendly dosing.

Commercially Available drug is an oral tablet and the compounded drug product is an oral capsule), FDA generally intends to consider the compounded drug to be Essentially a Copy of the Commercially Available drug. Notwithstanding the foregoing, even if the compounded drug has the same dosage form as a Commercially Available drug, such compounded drug will not be deemed Essentially a Copy if a prescriber determines that there is a change required which produces, for that patient or patient population, a significant difference from the Commercially Available drug product, which determination shall be deemed to exist if a veterinarian prescribes or orders such compounded drug product.[20]

[20] Examples of this include when a veterinarian prescribes a chewable dosage form when a capsule form is Commercially Available, when a compounded drug contains flavoring that could assist in compliance that the Commercially Available drug does not contain and when a Commercially Available drug contains excipients or allergens that a veterinarian determines are not appropriate for an animal patient.

Exhibit B

Serious Adverse Drug Experiences mean:

any adverse drug experience occurring at any dose that results in any of the following outcomes:

- Death,
- A life-threatening adverse drug experience,
- Inpatient hospitalization or prolongation of existing hospitalization,
- A persistent or significant disability/incapacity, or

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a Serious Adverse Drug Experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

A Serious Adverse Drug Experience is Unexpected when an adverse drug experience:

- has not been previously observed (i.e., included in the labeling of FDA approved drugs containing the same ingredients) or
- is symptomatically and pathophysiologically related to a previously observed adverse drug event, but differs from that event because of greater severity or specificity.

Each adverse drug experience received or otherwise obtained that is both serious and unexpected should be reported as soon as practicable, but in no case later than 30 calendar days of initial receipt of the information along with a copy of the drug product's current labeling. All serious, unexpected adverse drug experiences that are the subject of these reports must be promptly investigated and a follow-up report must be submitted within 30 calendar days of receipt of new information or as requested by FDA.

A Product Defect shall mean sterility failures, endotoxin failures, cross contaminations, and incorrect potency outside of an acceptable range.

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