GFI #256: The Ever-Changing Guidance Town Hall

Thursday, May 18, 2023
12:30 pm Eastern; 11:30 am Central;
10:30 am Mountain; 9:30 am Pacific

vetmeds.org/gfi256-town-hall

Reference

Contains Nonbinding Recommendations

#256

Compounding Animal Drugs from Bulk Drug Substances

Guidance for Industry

This version of the guidance replaces the version made available April 2022. This revision provides the approved information collection OMB Control No. 0910-0904.

Submit comments on this guidance at any time. 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 further information regarding this document, contact AskCVM@fda.hhs.gov.

Additional copies of this guidance document may be requested from the Policy and Regulations Staff (HFV-6), Center for Veterinary Medicine, Food and Drug Administration, 7500 Standish Place, Rockville, MD 20855, and may be viewed on the Internet at https://www.fda.gov/animal-veterinary, https://www.fda.gov/regulatory-information/search-fda-guidance-documents, or https://www.regulations.gov.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Veterinary Medicine
August 2022

OMB Control No. 0910-0904
Current expiration date available at https://www.reginfo.gov
See additional PRA statement in Section IV of this guidance.

Background

- Animal Medicinal Drug Use Clarification Act 1994 (AMDUCA)
  - § 530.13 Extralabel use
  - Applies to compounding of a product from approved animal or human drugs
  - Nothing in this part shall be construed as permitting compounding from bulk drugs

FDA Guidance Documents

- 1996 CPG 608.400
  - Revoked 2015
- 2015 GFI #230
  - Revoked 2017
- 2019 GFI #256 Draft
- 2022 GFI #256 Final

GFI #256 Scope

- Limits the use of animal drugs compounded from bulk drug substances to when there is no medically appropriate human or animal drug that is FDA-approved, conditionally approved, or indexed

GFI #256 Scope

- Intended to focus FDA's enforcement activities on most significant concerns, including compounded drugs that:
  - present particular human or animal safety concerns
  - are intended for use in food-producing animals
  - are copies of marketed FDA-approved or indexed drugs
  - are compounded without a patient-specific prescription (i.e., office stock)

GFI #256 Scope

- Circumstances FDA does not generally intend to take enforcement action for violations of requirements for approval, adequate directions, and cGMP
  - Compounding for Nonfood-Producing Animals: Patient-Specific Prescriptions
  - Compounding for Nonfood-Producing Animals: Without Patient-Specific Prescriptions
  - Drugs for Use as Antidotes for Food-Producing Animals or Sedatives and Anesthetics for Free-Ranging Wildlife Species

GFI #256 Requires

- Compounded by or under the direct supervision of a veterinarian or pharmacist in a state-licensed pharmacy or federal facility
- Compounded in compliance with state laws and regulations governing drugs, pharmacy, and veterinary medicine
- Bulk drug substances, inactive ingredients, and finished drug products used in compounding meet the standards set in any applicable USP-NF monograph and comply with other FD&C Act requirements for drug components
- Valid VCPR

Federal Law - FDAMA

- (b) Compounded Drug.--
- (1) Licensed pharmacist and licensed physician.--A drug product may be compounded under subsection (a) if the licensed pharmacist or licensed physician--
- (A) compounds the drug product using bulk drug substances, as defined in regulations of the Secretary published at section 207.3(a)(4) of title 21 of the CFR
- (i) that--
- (I) comply with the standards of an applicable United States Pharmacopoeia or National Formulary monograph, if a monograph exists, and the United States Pharmacopoeia chapter on pharmacy compounding;
- (II) if such a monograph does not exist, are drug substances that are components of drugs approved by the Secretary; or [Page 111 STAT. 2329]
- (III) if such a monograph does not exist and the drug substance is not a component of a drug approved by the Secretary, that appear on a list developed by the Secretary through regulations issued by the Secretary under subsection (d);
- (ii) that are manufactured by an establishment that is registered under section 510 (including a foreign establishment that is registered under section 510(i)); and
- (iii) that are accompanied by valid certificates of analysis for each bulk drug substance;

Federal Law - FDAMA

- (C) does not compound a drug product that appears on a list published by the Secretary in the Federal Register of drug products that have been withdrawn or removed from the market because such drug products or components of such drug products have been found to be unsafe or not effective; and
- (D) does not compound regularly or in inordinate amounts (as defined by the Secretary) any drug products that are essentially copies of a commercially available drug product.
- (2) Definition.--For purposes of paragraph (1)(D), the term `essentially a copy of a commercially available drug product' does not include a drug product in which there is a change, made for an identified individual patient, which produces for that patient a significant difference, as determined by the prescribing practitioner, between the compounded drug and the comparable commercially available drug product.
- (3) Drug product.--A drug product may be compounded under subsection (a) only if--
- (A) such drug product is not a drug product identified by the Secretary by regulation as a drug product that presents demonstrable difficulties for compounding that reasonably demonstrate an adverse effect on the safety or effectiveness of that drug product; and

Compounding for Nonfood-Producing Animals: Patient-Specific Prescriptions

Drug dispensed by

- Pharmacy, after receipt of a prescription for a specific patient directly to the prescribing veterinarian or to the patient's owner or caretaker
- Veterinarian to the owner or caretaker of a patient in his or her practice, or to another veterinarian in his or her practice located in the same physical location
- The enforcement discretion policy does not apply to compounded drugs that are dispensed or transferred to a third party such as a distributor or retailer, or by a pharmacy to a veterinarian who did not write the prescription

Compounding for Nonfood-Producing Animals: Patient-Specific Prescriptions

- Drug is not a copy of a marketed FDA-approved or indexed drug
  - Same active ingredient or active moiety
  - Same route of administration
- Or, if it is a copy, there is a difference that will produce a clinical difference in the identified patient as determined by the treating veterinarian
  - **Documentation**: Retain a copy of Rx on which veterinarian has noted the medical rationale or contact veterinarian to obtain medical rationale and note it on the prescription
  - If the prescribing veterinarian is compounding the drug, the medical rationale should be noted in the patient's medical record

Compounding for Nonfood-Producing Animals: Patient-Specific Prescriptions

Acceptable examples

- Patient is allergic to ingredient [X] in approved product
- [Ingredient name] in approved product is toxic to this species
- Patient would require too many tablets of the approved product
- Patient requires dose that would require a fraction of the approved tablet and tablet is not scored to accomplish this fractionated dose
- Patient cannot safely be pilled with the approved capsule

Compounding for Nonfood-Producing Animals: Patient-Specific Prescriptions

Unacceptable examples

- The compounded drug is less expensive
- Prefer [compounded drug/compounder]
- Need half strength (Approved product is 10 mg/ml solution, prescription is written for 10 ml dose of 5 mg/ml solution)

Compounding for Nonfood-Producing Animals: Patient-Specific Prescriptions

Document reason why approved drug can't be used as source of the active ingredient

- Chemical properties prevent its practical and effective use in the compounding of a specific drug
- An inactive ingredient is toxic to the target species
- The FDA-approved or indexed drug(s) that contains that active moiety is not available for compounding

Compounding for Nonfood-Producing Animals: Without Patient-Specific Prescriptions

- The veterinarian who stocks the drug dispenses or transfers it only to the owner or caretaker of the animal patient or to another veterinarian in the same practice
- The enforcement discretion policy described in this guidance does not apply to compounded drugs that are transferred to a third party such as a distributor, retailer, or veterinarian at another physical location

Compounding for Nonfood-Producing Animals: Without Patient-Specific Prescriptions

- Drug is intended for use in a nonfood-producing species
- 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*

DOGS, CATS, HORSES

Bulk Drug Substance (BDS)	Species	Dosage form(s)	Strength/concentration
Amlodipine besylate (1/19/2023)	**dog, cat**	oral solution	1.25 mg/ml
		oral suspension	1.25 mg/ml
		capsule	0.625 mg
		tablet	0.625 mg
		mini-tab	0.625 mg
Apomorphine hydrochloride (8/11/2016)	**dog**	solution for injection	2.5 mg/ml
Chloramphenicol (2/28/2023)	**horse**	oral suspension	15 - 500 mg/ml
		oral paste	100 - 500 mg/ml
Cisapride (9/6/2016)	**cat**	tablets or capsules	2.5 and 5 mg
		oral suspension	5-10 mg/ml
Cyclosporine (9/20/2022)	**horse**	ophthalmic ointment	1-2%
Gabapentin (9/29/2023)	**dog, cat**	oral suspension	50 mg/ml
Guaifenesin (11/9/2016)	**horse**	soluble powder to be reconstituted into a solution for IV infusion with the addition of 500 ml (10%) or 1000 ml (5%) sterile diluent	50 gm
Idoxuridine (2/1/2022)	**cat**	ophthalmic ointment or solution	0.1%

Itraconazole with DMSO (1/31/2022)	**horse**	ophthalmic ointment or solution	itraconazole 1%/DMSO 30%
Methocarbamol (3/29/2023)	**dog, cat**	oral suspension	30 - 300 mg/mL
Metronidazole benzoate (5/18/2018)	**cat**	oral suspension	80 mg/ml
Miconazole nitrate (11/23/2016)	**horse**	ophthalmic ointment or solution	1 - 2%
Mirtazapine (12/6/2022)	**dog, cat**	tablet	1.0 – 3.75 mg
		capsule	0.5 – 3.75 mg
Potassium bromide (12/21/2016)	**dog**	oral solution	250 mg/ml
Prazosin (2/28/2023)	**dog, cat**	tablet, flavored tablet	0.25 - 0.5 mg
		capsule	0.25 - 0.5 mg
		oral liquid/suspension	0.15 - 15 mg/ml
Rifampin (10/20/2022)	**horse**	oral suspension	100 mg/ml
Tacrolimus (11/23/2016)	**dog**	ophthalmic drops	0.01 - 0.03%
Thyrotropin-releasing hormone (3/8/2023)	**horse**	sterile powder	25 mg/vial
		sterile liquid	1 mg/mL

NONFOOD-PRODUCING MINOR SPECIES

Bulk Drug Substance (BDS)	Species	Dosage form(s)	Strength/concentration
Azaperone tartrate (2/1/2022)	**zoo animals, captive wildlife species, and laboratory animals**	suspension for injection	40 mg/ml
Buprenorphine HCl (4/24/2023)	**captive non-human primates, captive marine mammals**	injectable polymeric matrix solution	5.0 – 10 mg/mL
Diprenorphine (2/1/2022)	**zoo animals and captive wildlife species**	solution for injection	2 mg/ml
Etorphine hydrochloride (2/1/2022)	**zoo animals and captive wildlife species**	solution for injection	10 mg/ml
Ketamine hydrochloride (3/8/2022)	**zoo animals and captive wildlife species**	solution for injection	200 mg/ml
Medetomidine hydrochloride (2/1/2022)	**laboratory non-human primates, and zoo and captive wildlife animals**	solution for injection	10, 20, 40 mg/ml
Midazolam (2/1/2022)	**large zoo animals and captive wildlife species**	solution for injection	50 mg/ml
Tolazoline hydrochloride (2/1/2022)	**zoo animals and captive wildlife species**	solution for injection	200 mg/ml

Antidotes for Food-Producing Animals or Sedatives and Anesthetics for Free-Ranging Wildlife Species

- Veterinarian documents a scientifically based withdrawal time that ensures residues of the: (1) antidote, or (2) sedative or anesthetic are not present in the animal at the time of slaughter or harvest or the veterinarian ensures the animal does not enter the food supply

Antidotes for Food-Producing Animals or Sedatives and Anesthetics for Free-Ranging Wildlife Species

- Compounded from a bulk drug substance listed on FDA's *List of Bulk Drug Substances for Compounding Drugs for Use in Food-Producing Animals or Free-Ranging Wildlife Species*

FOOD-PRODUCING ANIMALS (ANTIDOTES)

Bulk Drug Substance (BDS)	Species	Dosage form(s)	Strength/concentration
Copper glycinate (1/31/2022)	beef calves and beef cattle	Injection	200 mg/ml

FREE-RANGING WILDLIFE SPECIES (SEDATIVES AND ANESTHETICS

Bulk Drug Substance (BDS)	Species	Dosage form(s)	Strength/concentration
Azaperone tartrate (2/1/2022)	free-ranging wildlife species	suspension for injection	40 mg/ml
Diprenorphine (2/1/2022)	free-ranging wildlife species	solution for injection	2 mg/ml
Etorphine hydrochloride (2/1/2022)	free-ranging wildlife species	solution for injection	10 mg/ml
Ketamine hydrochloride (3/8/2022)	free-ranging wildlife species	solution for injection	200 mg/ml
Medetomidine hydrochloride (2/1/2022)	free-ranging wildlife species	solution for injection	10, 20, 40 mg/ml

Labeling

Must comply with applicable state law(s) and include

- Drug name and strength
- BUD
- Species
- Pharmacy name, address, and contact information
- The statements,
  - Report suspected adverse reactions to the pharmacy and to FDA using online Form FDA 1932a
  - This is a compounded drug. Not an FDA approved or indexed drug
  - Caution: Federal law restricts this drug to use by or on the order of a licensed veterinarian

Labeling

Additionally, patient-specific labeling must include

- Patient identification (e.g. name, identifier for an individual animal or a group of animals)
- Name of prescribing veterinarian

Labeling

Additionally, office-stock labeling must include

- Name, address, and contact information of ordering veterinarian
- The statement, Not for use in food-producing animals

Labeling

Additionally, antidote labeling for food-producing animals and sedative and anesthetic labeling for free-ranging wildlife species must include

- Name, address, and contact information of veterinarian ordering the antidote or the wildlife health professional ordering the sedative or anesthetic
- Prescribing veterinarian-determined withdrawal time

Reporting

Upon becoming aware of any adverse event or product defect associated with a drug compounded from a bulk drug substance, the pharmacist or veterinarian who compounded the drug reports the event on Form FDA 1932a, which is available online, within 15 business days