FDA's New Guidance on Compounding Bulk Drug Substances

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U.S. FOOD & DRUG ADMINISTRATION
CENTER FOR VETERINARY MEDICINE

FDA Guidance on Compounding Bulk Drug Substances

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Guidance For Industry #256

Today's Presentation

Part I

- Will cover the three legal marketing statuses for animal drugs and pharmaceutical grade substances

Part II

- Will cover issues related to drug compounding and Guidance for Industry (GFI) #256

https://pixabay.com/vectors/compass-directions-north-south-159202/

Learning Objectives

- Explain the three legal marketing statuses for animal drugs: Approval, Conditional Approval, and Indexing
- Identify approved, conditionally approved, and indexed drug products
- Discuss pharmaceutical grade substanc vs indexed drugs

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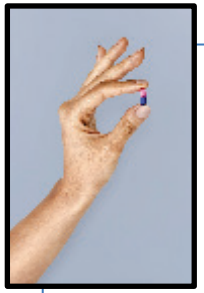
Definitions

Major species - horses, dogs, cats, cattle, pigs, chickens, and turkeys

Minor species - all other animals, other than humans, are considered minor by FDA



Minor use - drugs intended for use in major species for diseases that occur infrequently or in limited geographic areas and in only a small number of animals annually

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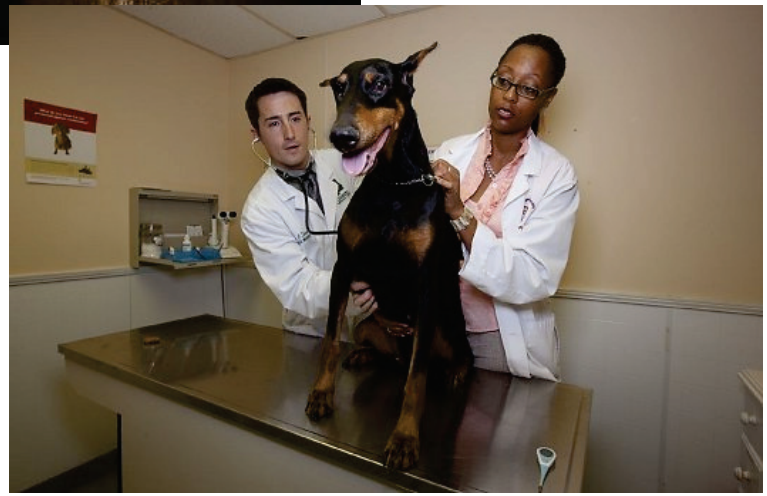
Important Note

In this presentation, the information provided on the three legal marketing statuses for animal drugs (approval, conditional approval, and indexed) is in relation to using drugs for the clinical care of animals, not when the drug is the subject of the research.



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What is the difference between FDA-approved, conditionally approved, and indexed drugs?

Approved Drugs

Adequate and well-controlled studies: Substantial evidence that drug is safe and effective for intended use

Environmental Safety, User Safety, and Human Food Safety

Manufacturing studies: strength, purity

Photo credit: Karolina Grabowska https://www.pexels.com/video/a-scientist-using-a-microscope-8539894/

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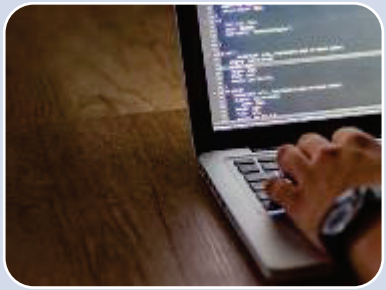
Approved Drugs



Data reviewed by FDA scientists

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Manufactured according to Good Manufacturing Practices (CGMPs); ensures quality, consistency

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Extra label use legal under certain circumstances

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Visit the FDA site to read the ins and outs of extra-label drug use in animals, including:

- Valid veterinarian-client-patient relationship
- General conditions for extra-label drug use
- Conditions for extra-label drug use in food-producing animals
- Compounding
- Drugs prohibited from extra-label uses in animals
- Judicious use of antimicrobials and extra-label drug use in food-producing animals

www.fda.gov/animal-veterinary/resources-you/ins-and-outs-extra-label-drug-use-animals-resource-veterinarians

How to Recognize Approved Drugs

ANADA 200-322, Approved by FDA
Net Contents: 50 mL

Label may have :

- New Animal Drug Application (NADA) number (6 digits)
- Abbreviated New Animal Drug Application (ANADA) number (generic drugs)
- Statement: “Approved by FDA”

If no NADA or ANADA number is listed, use this searchable database of approved animal drugs:
https://animaldrugsatfda.fda.gov/adafda/views/#/search

Conditional Approval

All approval requirements met except **effectiveness** (but reasonable expectation of effectiveness)

May be marketed up to 5 years (through annual renewals) while drug sponsor completes effectiveness section for full approval

Conditional Approval

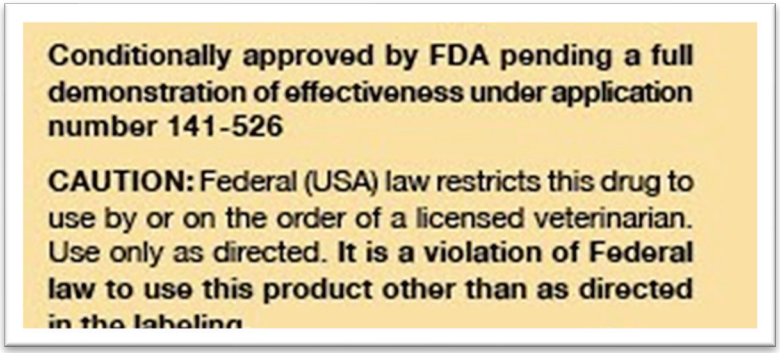
For:

minor uses in major species

minor species

Extralabel use is prohibited

How to Recognize Conditionally Approved Drugs



The drug label will contain a six-digit Conditional New Animal Drug Application number.

Indexed Drugs

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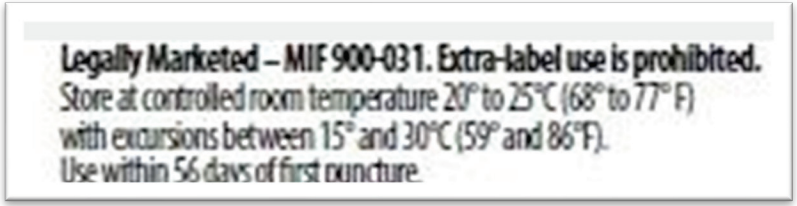
- Alternative to approval (legal marketing, NOT approval)
- Target animal safety and effectiveness via risk-benefit analysis by an outside expert panel
- FDA reviews summary of manufacturing process; user and environmental safety information
- Drug holder signs commitment to manufacture in accordance with CGMPs
- For non-food minor species only
- Extralabel use prohibited

How to Recognize Indexed Drugs


LEGAL STATUS—In order to be legally marketed, a new animal drug intended for a minor species must be Approved, Conditionally Approved, or Indexed by the Food and Drug Administration. THIS PRODUCT IS INDEXED—MIF 900-031. Extra-label use is prohibited.

Drug label includes 6-digit Minor Species Index File (MIF) number.


Legally Marketed – MIF 900-031. Extra-label use is prohibited.
Store at controlled room temperature 20° to 25°C (68° to 77°F) with excursions between 15° and 30°C (59° and 86°F).
Use within 56 days of first puncture.

Drug label includes required labeling statements regarding legal marketing status.

Indexed drug list with labeling and Freedom of Information (FOI) summary: www.fda.gov/animal-veterinary/minor-useminor-species/index-legally-marketed-unapproved-new-animal-drugs-minor-species

Are there any similarities between FDA-approved, conditionally approved, and indexed drugs?

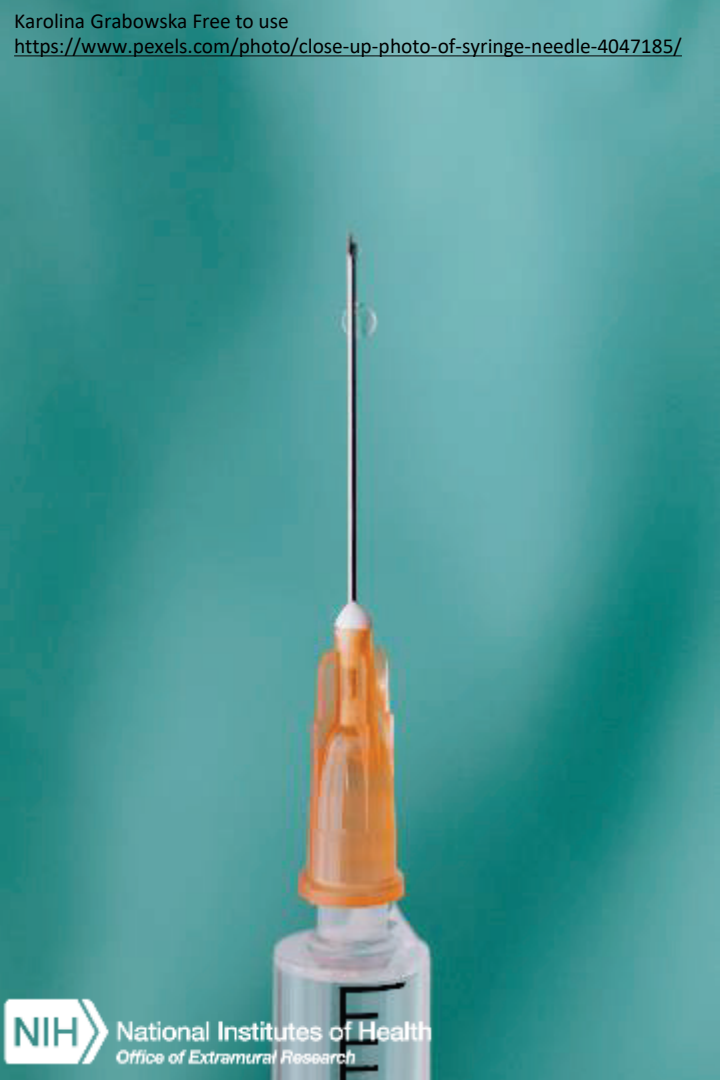
Similarities Between the Legal Marketing Statuses

All:

- Go through a pre-market process that includes FDA review of information related to the safety, effectiveness, and manufacturing

- Are monitored by the FDA once marketed
  - ✓ Approved drugs = inspection, annual reports, promotion, and advertising
  - ✓ Conditional approval = annual renewal process
  - ✓ Indexed drugs eligible for inspection, annual reports, promotion, and advertising

To report adverse events for any of these drugs: www.fda.gov/animal-veterinary/report-problem/how-report-animal-drug-and-device-side-effects-and-product-problems



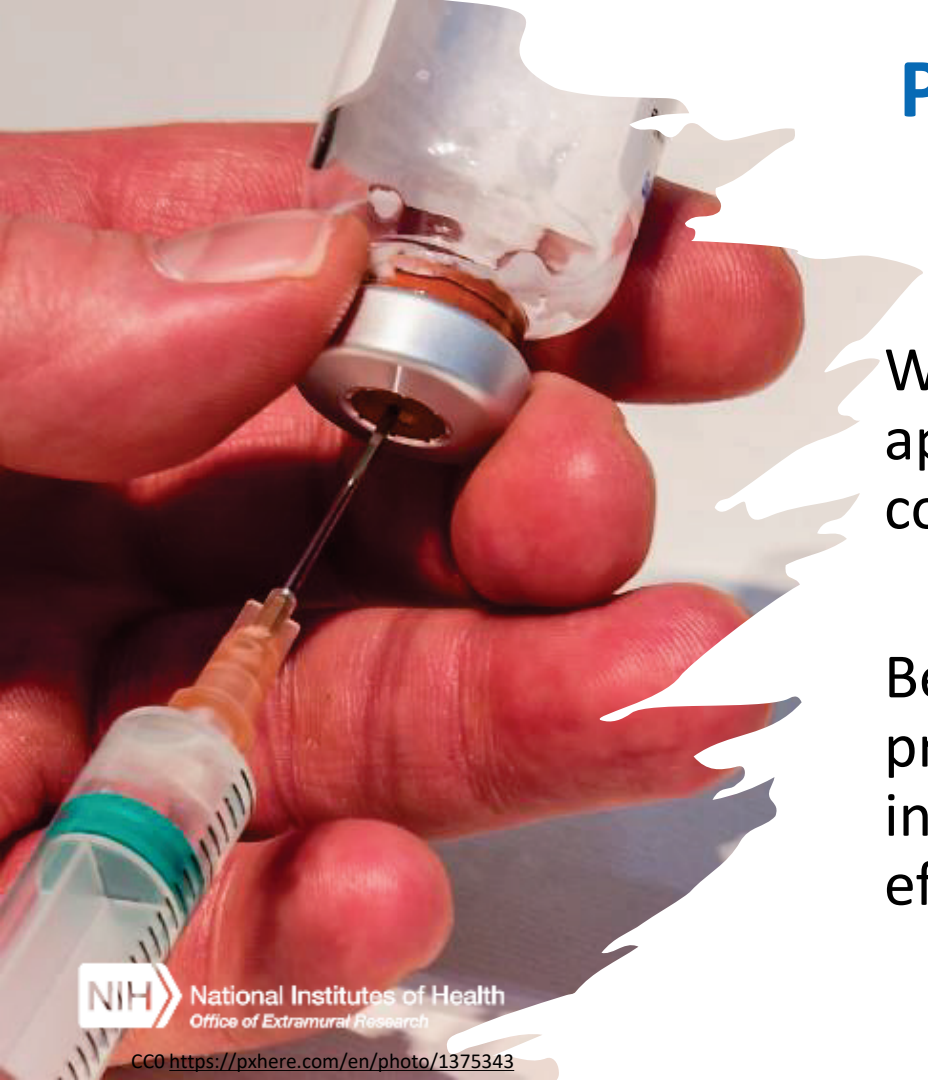
Pharmaceutical Grade vs Indexed Drugs

Pharmaceutical grade substance:

Any active or inactive drug, biologic, reagent, etc., manufactured under Good Manufacturing Practices (**GMP**) which is **approved, conditionally approved, or indexed** by the FDA

Or

For which a **chemical purity standard** has been written or established by a **recognized compendium** (e.g., United States Pharmacopeia-National Formulary [USP-NF], British Pharmacopeia [BP])

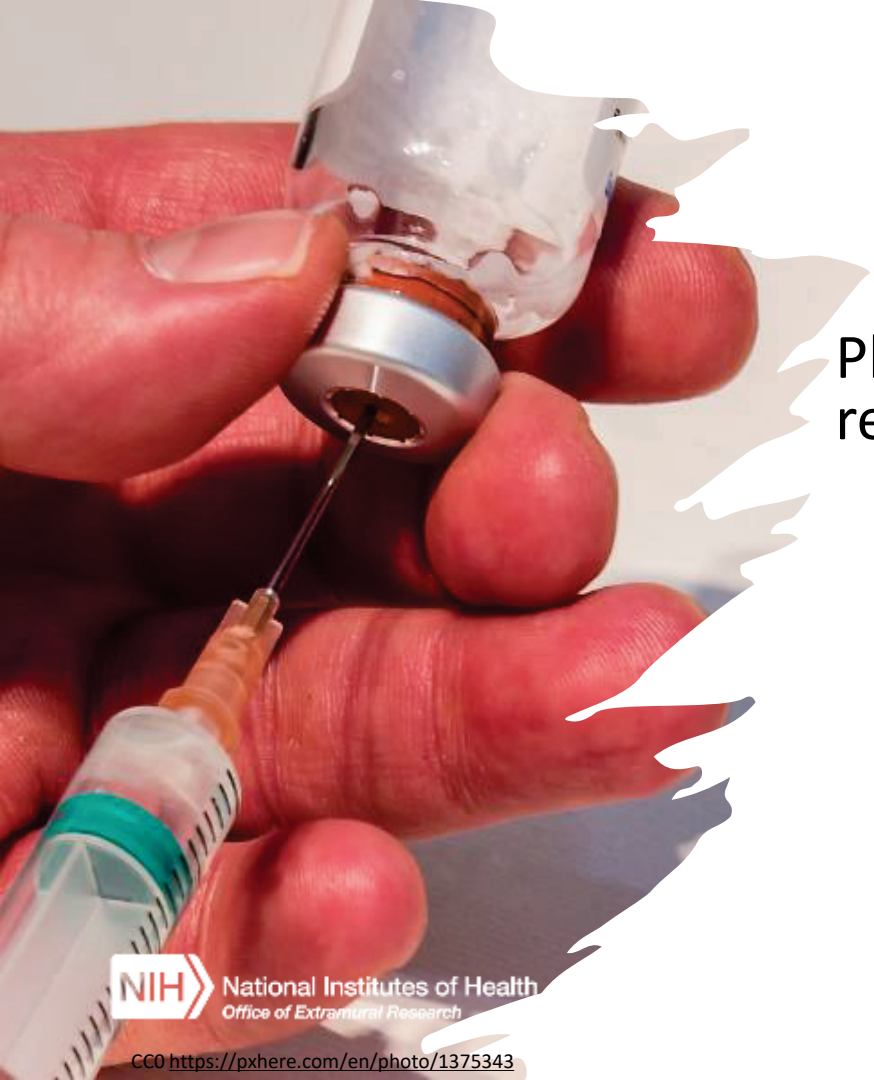


Pharmaceutical Grade vs Indexed Drugs

Why are FDA approved, conditionally approved and indexed drugs considered pharmaceutical grade?

Because all go through a pre-market process that includes FDA review of information related to the safety, effectiveness, and manufacturing.

National Institutes of Health
Office of Extramural Research



Pharmaceutical Grade Indexed Drugs

Pharmaceutical grade substance use requires:

- ✓adherence to FDA requirements when applicable
- ✓attention to appropriate reconstitution, labeling, storage, compounding, use, and administration.

NIH National Institutes of Health
Office of Extramural Research

Guidance for Industry #256 - Compounding Animal Drugs from Bulk Drug Substances

Today's presentation:

- **Approved** animal drugs vs **Unapproved** animal drug
- Compounding under the Animal Drug Use Clarification Act (**AMDUCA**)
- Compounding from Bulk Drug Substances (**BDS**)
- GFI #256 **Enforcement Discretion**
- **Lists** for Bulk Drug Substances
- GFI #256 **Education and Outreach**

Legally Marketed New Animal Drugs

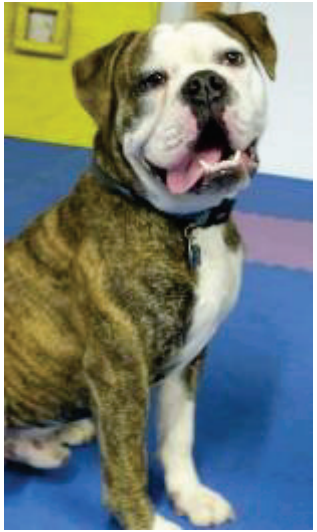
- FDA-approved
- Conditionally approved
- Listed on the *Index of Legally Marketed Unapproved Drugs for Minor Species*

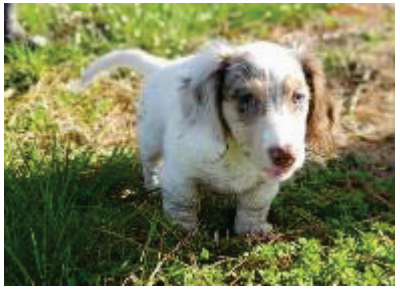
https://www.fda.gov/animal-veterinary/minor-useminorspecies/index-legally-marketed-unapproved-new-animal-drugs-minor-species

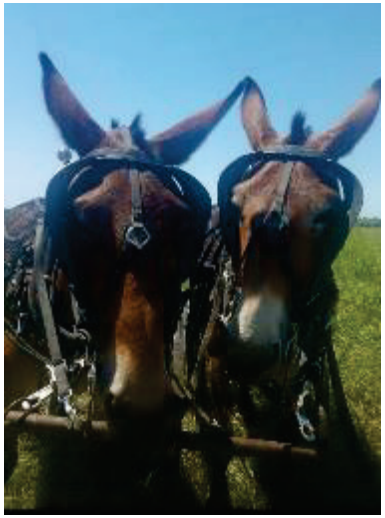
New Animal Drug Approvals

- **Pre-approval**: FDA *reviews data* demonstrating safety, efficacy, manufacturing quality, and labeling adequacy.
- **Post-approval**: FDA *monitors* adverse events, product defects, advertising, and changes in manufacturing and labeling.

Why vets need to compound animal drugs







Animal Drug Compounding

Animal drug compounding: process of combining, mixing or altering ingredients to create a medication tailored to the needs of an *individual animal* or a *small group of animals*.

Two categories, based on the source of the *active ingredient*.

1. Compounding from **FDA-approved** products (animal or human) = **legal extralabel use** under the AMDUCA of the FD&C Act. *This must be done under the supervision of a licensed vet or pharmacist!*
2. Compounding from **bulk drug substances (BDS):** Creates **unapproved new drug** under the FD&C Act

AMDUCA = Animal Medicine Drug Use Clarification Act
FD&C Act = Federal Food, Drug, and Cosmetics Act

What is the difference?

FDA-Approved Drugs

- **Pre-approval evaluation**
  - FDA evaluated and approved data demonstrating safety, efficacy, labeling, stability, and manufacturing
- **Post-approval monitoring**
  - Routine inspectional oversight
  - Post market monitoring of adverse events, product defects, and changes in manufacturing

Compounded Drugs

- **No pre-approval evaluation**
  - Unproven safety and bioavailability
  - Unknown effectiveness, quality, and stability
- **No post-approval monitoring**
  - No regulatory requirements to report adverse events or product defects

Concerns with Animal Drug Compounding

FDA is most concerned with drugs compounded from bulk drug substances (BDS) that:

Present human or animal **safety concerns**

Are for use in **food-producing animals**

Are **copies** of approved, conditionally approved, or indexed marketed animal drugs

Are compounded without a patient-specific prescription and sold to veterinarians as "**office stock**"

Concerns with Animal Drug Compounding

Animal safety concerns

- Adverse Events
- Recalls

Human food safety concerns

- Drugs compounded for use in food-producing animals

Copies

- Decrease incentives
- No pre-market evaluation or post-market monitoring

Office stock

- Could endanger large numbers of animals

Primary Objectives GFI #256

- Recognizing veterinarians' needs to access drugs to treat the broad diversity of animal patients
- Protecting animals and humans from unsafe animal drugs
- Preserving the integrity of the FDA animal drug approval process, which requires:
  - agency scientific review *before* approval, and
  - monitoring for continued safety and effectiveness *after* the drug is marketed.

Guidance for Industry #256

Outlines **enforcement discretion** for certain categories of animal drugs compounded from BDS:

- Patient specific prescriptions
  Not limited to a BDS list
- Office Stock for nonfood-producing species
- Antidotes for food-producing animals and sedatives for free-ranging wildlife

CVM GFI #256 - Compounding Animal Drugs from Bulk Drug Substances | FDA

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/cvm-gfi-256-compounding-animal-drugs-bulk-drug-substances

Changes From Draft to Final

Patient specific prescriptions

- Simplified the definition of a copy
- Clarified “medical rationale”
- Recommended reporting adverse events to compounder and FDA
- Additional labeling recommendations
- Allows compounding from indexed products

Changes From Draft to Final (Continued)

Office Stock for nonfood-producing species

- Streamlined nominations process
- Communication during nomination and review process
- Enforcement discretion during review
- Initial list of BDS for minor species

Food-producing animals

- Streamlined nominations process
- Adds free-ranging wildlife sedatives and anesthetics
- Initial list of BDS for antidotes and sedatives

Nominations to the Lists of Bulk Drug Substances

Nominations for Bulk Drug Substances for Compounding: (1) Office Stock Drugs for Use in Nonfood-Producing Animals or (2) Drugs for Use in Food-Producing Animals or Free-Ranging Wildlife Species | FDA
https://www.fda.gov/animal-veterinary/animal-drug-compounding/nominations-bulk-drug-substances-compounding-1-office-stock-drugs-use-nonfood-producing-animals-or-2

Office Stock for Nonfood Animals, Antidotes for Food Animals, and Sedatives for Free-ranging Wildlife

FDA intends to include a bulk drug substance on an "Office Stock List" if there is **NO**:

- **FDA-approved** or **indexed drug** that can be used as **labeled**,
- **FDA-approved** or **indexed drug** with the *same active ingredient* that can be used in an **extralabel** manner, and
- **Significant safety concern** specific to use of the BDS in animals.

Office Stock for Nonfood Animals

FDA intends to include a bulk drug substance on an "Office Stock List" if:

- It is needed **urgently to avoid animal suffering or death** (i.e., there's no time to wait for a prescription to be filled).

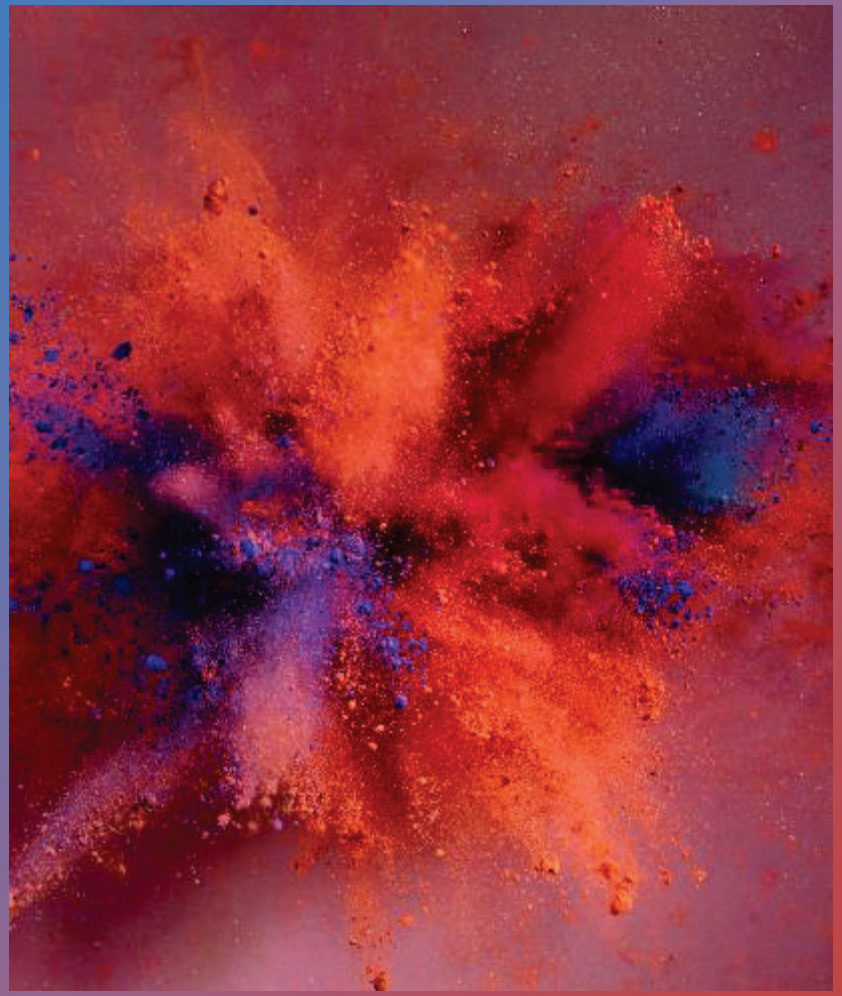
List of Bulk Drug Substances for Compounding Office Stock Drugs for Use in Nonfood-Producing Animals | FDA
https://www.fda.gov/animal-veterinary/animal-drug-compounding/list-bulk-drug-substances-compounding-office-stock-drugs-use-nonfood-producing-animals

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

FDA intends to include a bulk drug substance on a "Food-producing Animal List" if:

- The **compounded drug** is going to be used as an antidote in a food-producing animal, or as a sedative or anesthetic for free-ranging wildlife
- There is **scientific information to set a withdrawal, withholding, or discard time** for meat, milk, eggs, or other food derived from the treated animal(s) or the means to ensure that the animal does not enter the food

List of Bulk Drug Substances for Compounding Drugs for Use in Food-Producing Animals or Free-Ranging Wildlife Species | FDA
https://www.fda.gov/animal-veterinary/animal-drug-compounding/list-bulk-drug-substances-compounding-drugs-use-food-producing-animals-or-free-ranging-wildlife



What needs to be included in my nomination?

Information about the BDS and ***how*** it is used to treat animals.

Name of the BDS

- Chemical name
- Common name

Description of the drug to be compounded

- Dosage form (e.g., capsule, tablet, suspension)
- Strength or concentration (e.g., 25 mg/tablet, 50 mg/mL)
- Route of administration (e.g., oral, topical, injection, etc.)

Species to be treated

Disease or condition to be treated

Why it is needed to urgent treatment

- Only necessary for food-producing animals
- E.g., there's no time to wait for a prescription to be filled

What needs to be included in my nomination?

Information about ***why*** BDS is needed (if known):

- If there is no FDA-approved drug to treat the disease or condition, a statement that there is no approved drug option
- If an FDA-approved drug is available, explanation of why a compounded drug is needed
- If an FDA-approved drug with the same active ingredient is available, and explanation of why it can't be used to legally compound a drug

What needs to be included in my nomination?

Information about ***safety*** (if known):

Any animal or human safety concerns

If the drug is to be used as an antidote in a food-producing animal, or as a sedative or anesthetic for free-ranging wildlife, scientific evidence for determining a withdrawal, withholding, or discard time for meat, milk, eggs, or other food derived from the treated animal(s)

How do I submit a nomination?

Submit the nomination, including any attachments, to:

- Docket No. FDA-2018-N-4626, at https://www.regulations.gov.
- Or mail to: Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. Be sure to include the docket number.

*Note: If you have any questions while preparing or submitting your nominations, please contact CVM for assistance via email at: CVM Compounding@fda.hhs.gov

What happens after I submit my nomination?

FDA adds bulk drug substances that have been nominated and are under review to the List of Nominated Bulk Drug Substances Currently Under Review.

- Currently, FDA generally intends to refrain from taking enforcement action when these bulk drug substances currently under review are used to compound a finished drug as described in the nomination.
- Bulk drug substances will remain on this list only during FDA's initial review of their nomination.

https://www.fda.gov/animal-veterinary/animal-drug-compounding/bulk-drug-substances-currently-under-review

What happens after I submit my nomination?

After FDA completes its review, the bulk drug substance will be placed on one of these lists:

- Bulk Drug Substances Reviewed and Not Listed
  https://www.fda.gov/animal-veterinary/animal-drug-compounding/bulk-drug-substances-reviewed-and-not-listed
- List of Bulk Drug Substances for Compounding Office Stock Drugs for Use in Nonfood-Producing Animals,
  https://www.fda.gov/animal-veterinary/animal-drug-compounding/list-bulk-drug-substances-compounding-office-stock-drugs-use-nonfood-producing-animals
- List of Bulk Drug Substances for Compounding Drugs for Use in Food-Producing Animals or Free-Ranging Wildlife Species
  https://www.fda.gov/animal-veterinary/animal-drug-compounding/list-bulk-drug-substances-compounding-drugs-use-food-producing-animals-or-free-ranging-wildlife
- Should the bulk drug substance be placed on the list Bulk Drug Substances Reviewed and Not Listed, additional or new information can be submitted at any time for FDA's review.

More Nomination Information

- **Visit FDA's website**: Nominations for Bulk Drug Substances for Compounding: (1) Office Stock Drugs for Use in Nonfood-Producing Animals or (2) Drugs for Use in Food-Producing Animals or Free-Ranging Wildlife Species for more information.

- **Questions?:** If you have any questions while preparing or submitting your nominations, please contact CVM for assistance via email at: CVM Compounding@fda.hhs.gov

Implementation and Outreach

- Initial education and outreach period
  - Emphasis on stakeholder engagement
  - Additional webinars planned
  - Library of resources available
    - Q&As
    - Checklist for vets and pharmacists
    - Quick Reference for Nominations
- Shift emphasis to inspections in FY2023

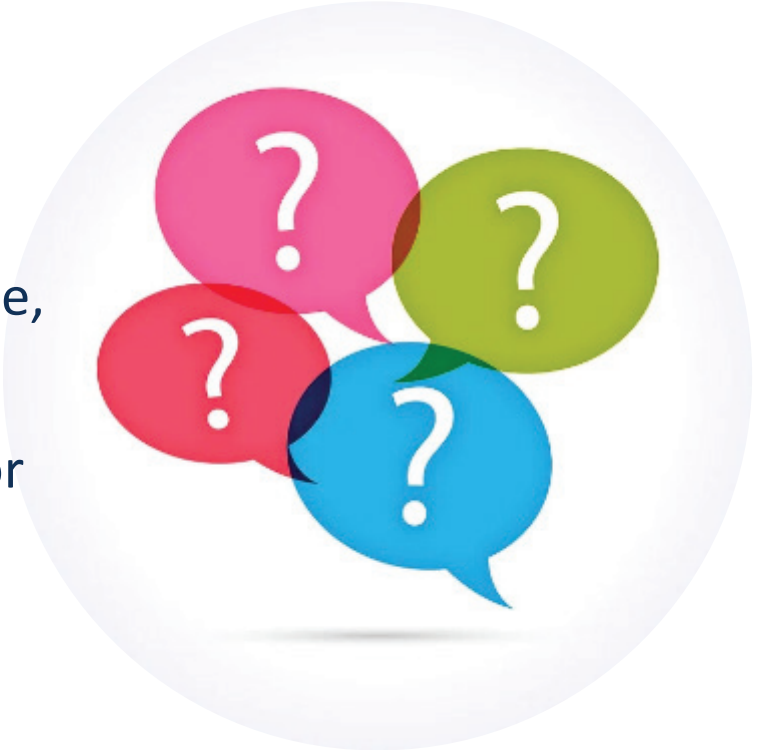
Key Points Under GFI 256

- Flexibility for veterinarians to compound animal drugs from BDS when FDA-approved options are not available.
- Prescribing drugs to be compounded from BDS for specific nonfood-producing patients isn't limited to an FDA bulk drug list.
- Nominations to the Lists (Office Stock for nonfood-producing animals and Antidotes and Sedatives for food-producing animals) remain open and FDA will continue to review nominations and update lists as needed.
- Please email CVMCompounding@fda.hhs.gov with any questions.

Question 1:

Can mouse buprenorphine be used in other related rodents such as wild mice, voles, or other non-*Mus* mice?

If the insert says for use in mice only or rats only and it is used in another species, is this off-label use or is it illegal?



Question 2:

If 2 pharmaceutical grade* drugs are mixed by a licensed veterinary compounding pharmacy, are they still considered pharmaceutical grade?

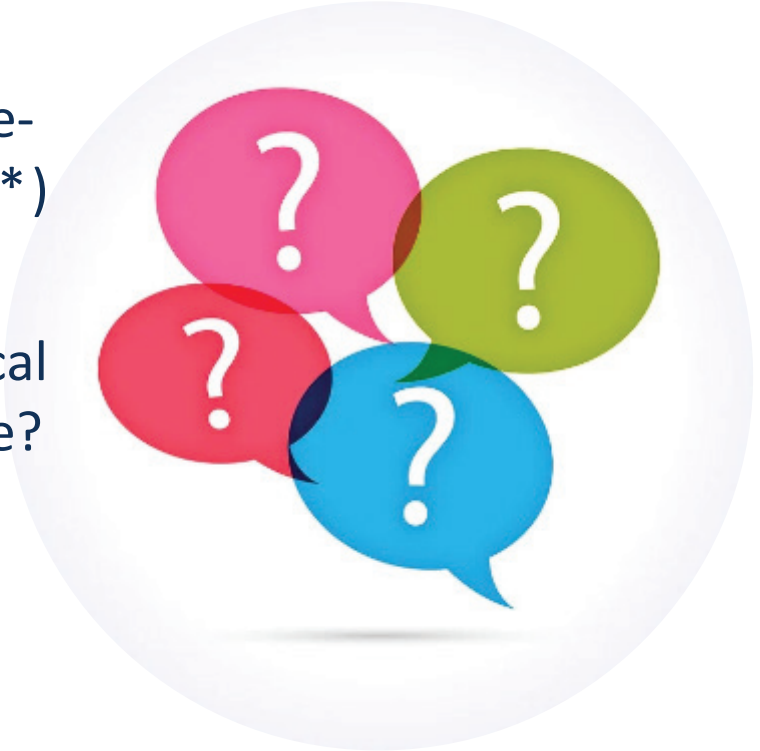
What if this is done by a university or hospital pharmacy? How about by the vet or PI?

*Any active or inactive drug, biologic, reagent, etc., manufactured under Good Manufacturing Practices (GMP) which is approved, conditionally approved, or indexed by the FDA

Question 3:

Is a cocktail such as ketamine-atropine-rompun (all vet pharmaceutical grade*) still pharma grade when combined?

If one component is not pharmaceutical grade*, would the mixture also not be?



*Any active or inactive drug, biologic, reagent, etc., manufactured under Good Manufacturing Practices (GMP) which is approved, conditionally approved, or indexed by the FDA

Question 4:

Is sterile dilution of pharmaceutical grade* drugs considered compounding?

If a pharmaceutical grade* diluent such as sterile saline or PBS is used to dilute a pharmaceutical grade* drug, is it still pharmaceutical grade* or does it need to be scientifically justified and approved by the IACUC?

What about drugs that are sold in vials with the diluent attached to lyophilized powder?

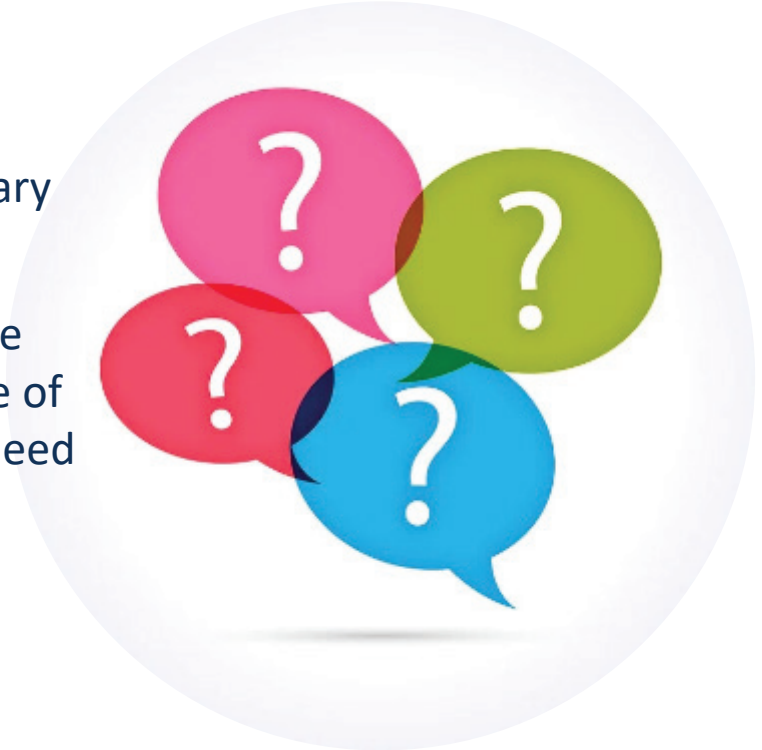
*Any active or inactive drug, biologic, reagent, etc., manufactured under Good Manufacturing Practices (GMP) which is approved, conditionally approved, or indexed by the FDA

Question 5:

A PI has received FDA approval for an Investigational New Animal Drug (INAD) Application that proposes to administer a dietary supplement (non-USP grade) on study.

Does that FDA approval confer some USP-grade designation to the supplement for the purpose of administration to animals, or does the PI still need to justify use of a non-pharmaceutical grade substance?

Does the FDA approval for the INAD mean the supplement is “conditionally approved” ?



Question 6:

What is the status of buprenorphine and other analgesics as to shortages due to FDA enforcement actions?

Animaldrugshortages@fda.hhs.gov

Question 7:

Please comment on Buprenorphine SR (Ethiqa) availability currently.

A statement was made that “a pharmaceutical grade sustained-release compound is available but the supply is sufficiently unreliable to be unavailable.”

Is Zoopharm from Wedgewood pharmaceuticals (a compounding pharmacy) an option?

Question 8:

Is OLAW enforcing the use of Ethiqa (FDA-indexed) over the compounded buprenorphine-SR?

Is buprenorphine SR through the likes of ZooPharm acceptable for research animal use (for FDA? for OLAW?)

ZooPharm is a veterinary compounding pharmacy. Is use of Ethiqa preferred as it is not compounded and developed for mice and rats?

Question 9:

The manufacturer of buprenorphine SR (ZooPharm formulation) has an expiration date of at least six months but also a note to discard 28 days after (vial) puncture. Which takes precedence?

OLAW and USDA ask institutions to follow manufacturer recommendations to discard after 28d unless there is an IACUC-approved reason to deviate.

There is a 2022 JAALAS paper demonstrating extended sterility.

What is FDA's take on this?

Question 10:

I have heard from a clinician that Buprenorphine SR has been reported to be causing abscesses at the injection site. Any reports to FDA on this?

Question 11:

We have just received a report that CO_2 supplies for euthanasia are currently low.

Does FDA have any comments on availability of medical grade gasses?

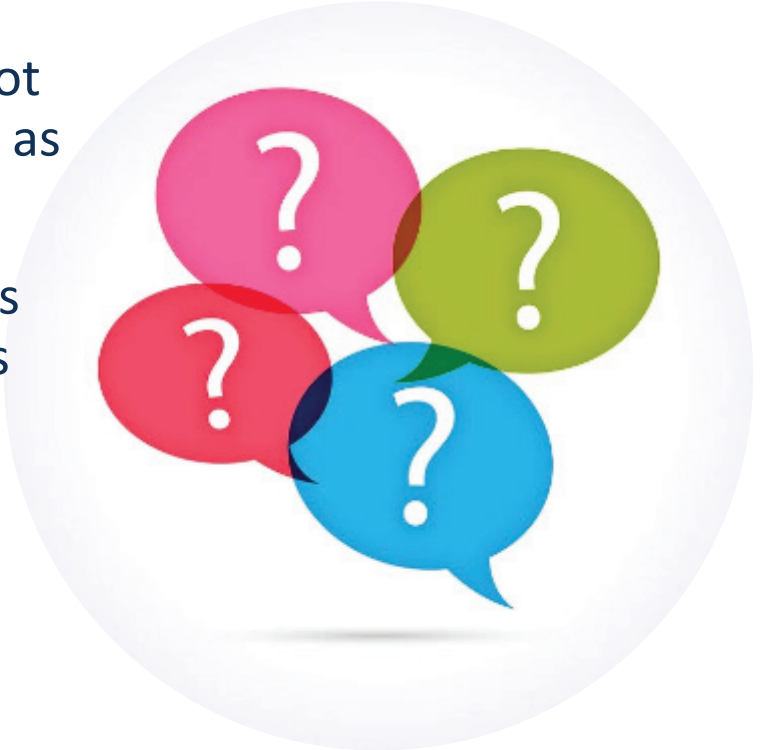
For oxygen, we have been advised in the past that welding grade gasses are often superior to medical grade as impurities would harm the stability of a welded joint so the quality control is even better.

Question 12:

What does it mean that a product is not approved by FDA but legally marketed as an indexed product?

Is this just because it is a minor species drug and hasn't gone through rigorous review?

Should we assume the FDA index designation is enough to allow use without IACUC approval for non-pharmaceutical grade products?



Email: ASKCVM@fda.hhs.gov

Next Webinar: Winter 2022
Topic TBD