



## FDA Proposed Guidance Document

### *Compounding Animal Drugs from Bulk Drug Substances*

May 19, 2015

#### Overview

Current law does not permit compounding of animal drugs from bulk drug substances, but the Food and Drug Administration recognizes that there are limited circumstances when an animal drug compounded from bulk drug substances may be an appropriate treatment option. According to the FDA, a “bulk drug substance” applies to “any substance that is represented for use in a drug and that, when used in manufacturing, processing or packaging of a drug, becomes an active ingredient or a finished dosage form of the drug.”

On May 19, 2015, the FDA released a draft guidance document that proposes a new enforcement policy related to the compounding of veterinary preparations using bulk ingredients. This draft document, [FDA's Guidance for Industry #230, “Compounding Animal Drugs from Bulk Drug Substances.”](#) outlines specific conditions under which the agency generally does not intend to take action against state-licensed pharmacies, veterinarians, and facilities registered as outsourcing facilities when drugs are compounded for animals from bulk drug substances.

GFI #230 will not become enforceable or official until a public comment period has closed and a final version is issued. Even then, it only represents the FDA's current thinking on this topic, which the agency will use as a baseline for determining whether to pursue enforcement action against undesirable compounding activities.

The veterinary profession and other stakeholders have 90 days to review and submit comments and questions to the FDA. The comment period for feedback on the overall guidance document is scheduled to close Aug. 17. The FDA is accepting nominations of bulk drug substances which can be used by outsourcing facilities through Nov. 16.

The AVMA has prepared the following summary for you, which contains key information on GFI #230. While the AVMA prepares to file formal comments on behalf of its members, we strongly encourage you to read through the draft guidance document and consider how its contents may affect your practice and how you care for your patients. Also, please review the questions at the end of this document and be sure to share your concerns and/or comments on those via e-mail with the AVMA or directly to the FDA.

By reading through GFI #230 and submitting your comments, you have an opportunity to shape how the FDA regulates compounding from bulk ingredients in the future. If you have

#### Deadlines:

**Aug. 17, 2015:** The comment period closes for feedback on the overall guidance document.

**Nov. 16, 2015:** The comment period closes for nominations of bulk drug substances which can be used by outsourcing facilities on FDA's proposed list.

#### Web Resources:

- [FDA's draft Guidance for Industry #230, “Compounding Animal Drugs from Bulk Drug Substances”](#)
- [The Federal Register notice from May 19, 2015](#)
- [Information on how to nominate bulk ingredients to the 503B outsourcing facility “positive list” of animal drugs](#)
- [AVMA's policies on compounding](#)

# Overview of FDA’s Proposed Guidance for Industry #230

## Bulk Ingredient Compounding In a State-Licensed Pharmacy

Pages 3-5 of the Proposed Guidance Document Policy III (A) (1-11)

### Highlights

- Compounding must be done by or under the direct supervision of a pharmacist.
- Any bulk ingredient used to compound must come from an FDA-registered manufacturer and have a valid certificate of analysis (COA).
- All compounding must follow the standards of USP <795> for non-sterile preparations and USP <797> for sterile preparations.
- All product defects or serious adverse events associated with a bulk-compounded veterinary preparation must be reported on [Form 1932a](#) within 15 days to the FDA.
- The preparation label must include: the name of the animal patient, the name of the owner/caretaker, and the species of the animal.
- The compounded product may not be sold or transferred by any other entity—meaning that the product cannot be wholesaled. This does not prevent a pharmacy from dispensing an order related to a patient-specific prescription.
- No compounding from bulk ingredients is permitted for food-producing animals.
- **The prescription and/or documentation from the veterinarian must have the following statement:** “This patient is not a food-producing animal.”
  - “Food-producing animals” are defined as all cattle, swine, chickens, turkeys, sheep, goats, and non-ornamental fish, regardless of whether the specific animal or food from the animal is intended to be introduced into the human or animal food chain (e.g. pet pot-bellied pigs, pet chicks).
  - The definition also includes any other animal which the veterinarian designates on the prescription as a food-producing animal regardless of species (e.g. rabbits, captive elk and deer).

### No Office-Use Compounding Permitted

- Compounding with bulk ingredients must be patient-specific. Dispensing to the patient is permitted only after a valid

prescription has been received by the pharmacy.

### Compounding “Marketed” Drugs

- If an FDA-approved animal or human drug exists, the pharmacy may compound a preparation using bulk ingredients of the same active ingredient only if there is a change between the compounded drug and the comparable FDA-approved animal or human drug made for an individually identified animal patient that produces a clinical difference for the individual patient as determined by the veterinarian prescribing the compounded drug.

### Documentation and Mandatory Statements

- The species of the animal being treated must be documented either on the prescription or other materials and be recorded by the pharmacist.
- If an FDA-approved animal or human drug with the same active ingredients exists and the pharmacist determines that the compound cannot be made using those ingredients, the pharmacist must document the reasoning for that (e.g., sterile injectable guaifenesin for equine use cannot be made from an over-the-counter cough syrup).
- **On the prescription or other documentation, the following statement must be included by the veterinarian:** “There are no FDA-approved animal or human drugs that can be used as labeled or in an extra-label manner under section 512(a)(4) or (5) and 21 CFT part 530 to appropriately treat the disease, symptom, or condition for which this drug is being prescribed.”
- If bulk ingredients are used to prepare a compound that contains the same active ingredient as an FDA-approved animal or human drug, it must be for a specific individual animal patient under the prescribing veterinarian’s care. **The prescription or documentation must be accompanied by a statement from the veterinarian stating** that the compounded preparation “produces a clinical difference for the individually identified animal patient” with an explanation of what that difference is.

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### Bulk Ingredient Compounding By a Licensed Veterinarian

Pages 5-6 of the Proposed Guidance Document Policy III (B) (1-9)

#### Highlights

- Compounding must be done by the veterinarian for an individual patient under his or her care.
- No compounding for food-producing animals by a veterinarian is permitted. (See the definition above for what constitutes a food-producing animal.)
- If an FDA-approved animal or human drug exists, the veterinarian may compound a preparation with the same active ingredient as the approved product using bulk ingredients *only if there is a change made that produces a clinical difference* for that individually identified animal patient under the veterinarian’s care.
- Bulk ingredient compounding is not permitted if there is any FDA-approved animal or human drug that can be used as labeled or in an extra-label manner to appropriately treat the disease, symptom or condition.
- All veterinarians engaged in compounding must follow the standards of USP <795> for non-sterile preparations and USP <797> for sterile preparations.
- Any bulk ingredient used to compound must come from an FDA-registered manufacturer and have a valid certificate of analysis.
- All product defects or serious adverse events associated with a compounded veterinary preparation from a bulk ingredient must be reported on [Form 1932a](#) within 15 days to the FDA.
- The preparation label must include the name of the animal patient, the name of the owner/caretaker, and the species of the animal.
- The veterinarian may not sell or transfer any compound prepared using bulk ingredients (e.g., to another clinic or another veterinarian). The veterinarian is permitted to use those compounds for administration to the individual animal patient or dispensing to that animal patient’s owner or caretaker.

### Bulk Ingredient Compounding By a 503B Outsourcing Facility

Pages 6-8 of the Proposed Guidance Document Policy III (C) (1-10)

#### Highlights

- Outsourcing facilities registered with the FDA are permitted to compound and distribute non-patient-specific veterinary preparations (i.e., office stock), but only using bulk drug substances which will appear on Appendix A of the guidance.
- Compounding must be done by or under the direct supervision of a pharmacist.
- Any bulk ingredient used to compound must come from an FDA-registered manufacturer and have a valid certificate of analysis.
- All compounding (sterile and non-sterile) conducted by a 503B outsourcing facility must comply with cGMP standards that the FDA is developing specifically for outsourcing.
- All product defects or serious adverse events associated with a bulk ingredient-compounded veterinary preparation must be reported on [Form 1932a](#) within 15 days to the FDA.
- No bulk ingredient-based compounding for food producing animals is permitted. **The prescription, order or other documentation from the veterinarian must have the following statement:** “This drug will not be dispensed for or administered to food-producing animals.” (See for the definition above for what constitutes a food-producing animal.)
- The compounded product may not be sold or transferred by any other entity—meaning that the product cannot be wholesaled. This does not prevent an outsourcing facility from filling an order from a veterinarian (i.e., office stock) for administration of the product to a patient in his or her care.
- All drugs compounded for animals must be reported by a 503B outsourcing facility on its biannual report to the FDA. It must list: the active ingredients; bulk ingredient source; assigned National Drug Code (NDC), where available; strength per unit; dosage form; route of administration; package description; and the quantity of units produced. The report must clearly designate which products were

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intended for animal use.

- **All orders from veterinarians, including prescriptions, must include a statement** confirming that the product is to be used in a manner and on a species that complies with the list of permitted bulk ingredient uses under Appendix A.

### Positive List

Because Section 503B of the [Drug Quality and Security Act of 2013](#) restricts the “what” and “when” of using a bulk ingredient by an outsourcing facility, the FDA is proposing a new process for nominating bulk substances that may be used by an outsourcing facility in compounding drugs for use in animals.

- The FDA issued a request for nominations of bulk ingredients at the same time the draft guidance document was released. The deadline for nominations is **Nov. 16, 2015**.
- Nominated bulk ingredients for animal compounding by 503B outsourcing facilities will need to provide information that shows:
  - No marketed, conditionally approved or index-listed animal drug is available to treat the specific condition.
  - No marketed, approved or human drug exists that could be used to treat the condition.
  - The drug cannot be compounded using an approved animal or human-finished manufactured drug product.
  - Use of a bulk ingredient compound is needed to prevent animal death or suffering.
  - No significant safety concerns exist that are associated with using a bulk ingredient for compounding.
- The FDA will review the nominated bulk list on a rolling basis and periodically update Appendix A. The actual frequency of the review and update timeline is not specified in the guidance document.

### Labeling Requirements

- The labeling of animal drugs compounded using bulk ingredients by outsourcing facilities must include:
  - Active ingredients, inactive ingredients, dosage form, strength, flavoring (if any), directions for use, quantity/volume, lot/batch number, date of compounding, Beyond-Use-Date, name of veterinarian who ordered or

prescribed the drug, address and phone number of the outsourcing facility.

- A clear statement that says, “Not for resale.”
- A statement, “For use in [species, condition, and limitations].”
- The statement, “Compounded by [name of 503B outsourcing facility].”
- The statement, “Adverse events associated with this compounded drug should be reported to the FDA on Form FDA1932a.”
- If the drug is being dispensed based upon the receipt of patient specific prescription, the name of the animal, the animal owner/caretaker’s name, and the species must be included.

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### Specific Veterinary-Related Questions Posed in the Guidance Notice

The FDA specifically seeks comments from the public on a number of questions, including the following:

- Should the final guidance address the issue of FDA-approved animal and human drugs that are in shortage or are otherwise unavailable? If so:
  - How should these situations be addressed in the final guidance?
  - How should the final guidance define “shortage” and “unavailable?”
  - What criteria should the FDA use to determine if an approved animal drug is in shortage or otherwise unavailable?
- Should licensed veterinarians be able to sell or transfer an animal drug compounded from bulk drug substances by a state-licensed pharmacy or an outsourcing facility to owners or caretakers of animals under the veterinarian’s care?
- Is additional guidance needed to address the compounding of animal drugs from approved animal or human drugs under sections 512(a)(4) or (a)(5) of the FFDCFA and 21 CFR Part 530?
- Is additional guidance needed to address the compounding of animal drugs from bulk drug substances for food-producing animals?
- Do United States Pharmacopeia and National Formulary (USP–NF) chapters <795> and <797> provide suitable standards for animal drugs compounded by veterinarians, and if not, what standards of safety, purity, and quality should apply to animal drugs compounded by veterinarians?
- How should the FDA apply the condition to identify an individual patient when it is not possible to identify an individual animal (e.g., koi in a koi pond)?
- Should facilities registered as “outsourcing facilities” be able to compound animal drugs from bulk drug substances that do not appear on Appendix A for an individually identified animal patient under conditions similar to those applicable to state-licensed pharmacies?
- The FDA is proposing that licensed pharmacies and veterinarians report any product defect or serious adverse event within 15 days of becoming aware of the product defect or serious adverse event.
  - How many licensed veterinarians compound animal drugs from bulk drug substances and would potentially be reporting product defects and serious adverse events to the FDA?
  - Are veterinarians reporting the same or similar information to any state regulatory agency?
  - If so, how many reports on average does each veterinarian submit each year?
  - How should the FDA define the terms “product defect” and “serious adverse event”?
- Can the FDA achieve the same objective of identifying and tracing the source of injuries or disease associated with an animal drug compounded from bulk substance through means other than product defect and serious adverse event reporting and if so, what other means?
- Is additional guidance needed to address the repackaging of drugs for animal use?
  - How widespread is the practice of repackaging drugs for animal use?
  - What types of drugs are repackaged for animal use, and why are they repackaged?
  - Have problems been identified with repackaged drugs for animal use?