

FDA Issues Draft Guidance on Use of Bulk Substances In Compounding For Animal Patients

On May 19, 2015 the Center for Veterinary Medicine of the Food and Drug Administration (FDA CVM) issued a draft Guidance for Industry (GFI) #230 *Compounding Animal Drugs From Bulk Drug Substances* and rescinded Compliance Policy Guide (CPG) 608.400 *Compounding of Drugs For Use In Animals*. CPG 608.400 has been in effect since its inception in 1996 and was revised in 2003. FDA CVM issued GFI #230 in response to sweeping changes in compounding regulation caused by the Drug Quality and Security Act of 2013 in order to bring regulatory enforcement for animal compounding more in line with that for humans. GFI #230 now represents FDA CVM's current thinking on use of bulk drug substances when compounding for non-human patients.

Summary of Key Points:

- The draft has a 90 day public comment period, closing August 17, 2015. Note: The American Veterinary Medical Association has requested a 90 day extension on the public comment period for the solicitation of bulk drug substances which, if granted, would extend the deadline for that notice to November 15, 2015.
- Guidances for Industry, even when official, contain non-binding recommendations regarding FDA's current thinking. GFI #230 describes circumstances under which FDA does not generally intend to initiate enforcement action against State-licensed pharmacies, licensed veterinarians, and facilities registered as outsourcing facilities under section 503B of the FD&C Act (outsourcing facilities) that compound animal drugs from bulk drug substances.
- GFI #230 addresses three areas of compounding using bulk drug substances for animal patients:
 - **By licensed pharmacies:**
 - Compounding must be performed by or under the direct supervision of a licensed pharmacist
 - The prescription must be for an individual patient.
 - The compound may only be prepared in advance of prescription receipt (anticipatory compounding) based on historical activity for that compound over a 14 day period in the previous 6 months.
 - The species of the patient, patient name and caretaker information must be stated on the prescription and the label.
 - Bulk drug substances may NOT be used to compound for food producing animals which are all cattle, swine, chicken, turkey, sheep, goats, and non-ornamental fish regardless of the intended use of the animal (i.e. chickens and pot-bellied pigs are always considered food producing animals by FDA even if they are considered pets by their owners).
 - Statements from the prescriber as to:
 - Why the compounded bulk drug substance will produce a desired clinical effect that an FDA approved product will not.
 - That "There are no FDA-approved animal or human drugs that can be used as labeled or in an extralabel manner under section 512(a)(4) or (5) and 21 CFR part 530 to appropriately treat the disease, symptom, or condition for which this drug is being prescribed."
 - **Note:** FDA estimates that this effort will take approximately 30 seconds per above item per prescription for each of an anticipated 6,350,000 veterinary compounded prescriptions annually.

- A pharmacy can compound from bulk drug substance if it is determined that the compounded drug cannot be made from the FDA-approved drug.
- The bulk drug substance must be obtained from an FDA registered supplier and accompanied by a certificate of analysis
- Must be compounded in compliance with USP Chapters <795> for non-sterile compounds and <797> for sterile compounds
- The compound may only be sold to the patient for whom it was prescribed and compounded and may not be resold by a third party (e.g. dispensed to a veterinarian who will then dispense or sell it to another patient).
- Any arising adverse effects from the compound must be reported within 15 days by the pharmacy on Form FDA 1932a. Form FDA 1932a can be downloaded at <http://www.fda.gov/downloads/aboutfda/reportsmanualsforms/forms/animaldrugforms/ucm048817.pdf>.
- **By licensed veterinarians:**
 - Must be prepared and dispensed by the veterinarian under the same conditions as stated above for pharmacists.
- **By licensed 503B outsourcing facilities:**
 - The drugs are compounded only from bulk drug substances appearing on Appendix A (a positive list potentially to be developed by an advisory committee) of this draft guidance.
 - The drug is compounded by or under the direct supervision of a licensed pharmacist.
 - The prescription or order, or documentation accompanying the prescription or order, for the drug contains the statement, "This drug will not be dispensed for or administered to food-producing animals."
 - The drug is compounded in accordance with cGMP requirements.
 - The bulk drug substance must be obtained from an FDA registered supplier and accompanied by a certificate of analysis
 - May only be administered to patients in the veterinarian's practice and may not be dispensed or resold to a third party.
 - Any arising adverse effects from the compound must be reported within 15 days by the outsourcing facility on Form FDA 1932a. Form FDA 1932a can be downloaded at <http://www.fda.gov/downloads/aboutfda/reportsmanualsforms/forms/animaldrugforms/ucm048817.pdf>.
 - All drugs compounded for animals by an outsourcing facility must be reported separately from drugs compounded for humans to the FDA each June and December providing
 - the active ingredient(s);
 - source of the active ingredient(s);
 - NDC number of the source ingredient(s),
 - if available; strength of the active ingredient(s) per unit;
 - the dosage form and route of administration;
 - the package description;
 - the number of individual units produced;
 - the NDC number of the final product, if assigned.

- The veterinarian's prescription or order states that the drug is intended to treat the species and condition(s) for which the substance is listed in Appendix A.
- The label of the drug includes the following:
 - Active ingredient(s).
 - Dosage form, strength, and flavoring, if any.
 - Directions for use, as provided by the veterinarian prescribing or ordering the drug.
 - Quantity or volume, whichever is appropriate.
 - The statement "Not for resale."
 - The statement "For use only in [fill in species and any associated condition or limitation listed in Appendix A]."
 - The statement "Compounded by [name of outsourcing facility]." h. Lot or batch number of drug.
 - Special storage and handling instructions.
 - Date the drug was compounded.
 - Beyond use date (BUD) of the drug.
 - Name of veterinarian prescribing or ordering the drug.
 - The address and phone number of the outsourcing facility that compounded the drug.
 - Inactive ingredients.
 - The statement "Adverse events associated with this compounded drug should be reported to FDA on a Form FDA 1932a."
 - If the drug is compounded pursuant to a patient specific prescription, the species of the animal patient, name of the animal patient, and name of the owner or caretaker of the animal patient.

Interested stakeholders are invited to provide public comments on the draft guidance to FDA by August 17, 2015. Bulk drug substance candidates for the Appendix A "positive list" for 503B outsourcing facilities should also be submitted to FDA by August 17, 2015.

Download the draft guidance document here:

<http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM446862.pdf>

The formally published documents appeared in the May 19, 2015 *The Federal Register* and can be reviewed in detail here:

<https://www.federalregister.gov/articles/2015/05/19/2015-11982/compounding-animal-drugs-from-bulk-drug-substances-draft-guidance-for-industry-availability>

Information on how to nominate bulk ingredients to the 503B outsourcing facility "positive list" of animal drugs appears here:

<https://www.federalregister.gov/articles/2015/05/19/2015-11983/list-of-bulk-drug-substances-that-may-be-used-by-an-outsourcing-facility-to-compound-drugs-for-use>

For further information see Frequently Asked Questions below.

Frequently Asked Questions:

Q: Is it now legal to compound with bulk drug substances for animal patients?

A: No. The guidance does not “legalize” use of bulk drug substances to compound for non-human patients, but instead provides non-binding recommendations as to circumstances when FDA will ordinarily not pursue regulatory enforcement against pharmacists or veterinarians providing bulk substance compounds for non-human patients.

Stakeholders should be aware that, until this draft is finalized, FDA intends to look at the totality of the circumstances when determining whether to take enforcement action for unlawful animal drug compounding activities.

Q: Do veterinarians now have to comply with USP Compounding Chapters <795> and <797> when compounding with bulk drug substances?

A: Yes. GFI #230 indicates that FDA will initiate regulatory enforcement against veterinarians not compounding in compliance with relevant USP compounding standards.

Q: Does this guidance apply to compounds prepared for non-human patients if the starting ingredients are FDA approved drugs?

A: No. Compounds prepared for non-humans from FDA approved products are not the subject of this guidance and are subject to the regulations promulgated to enforce the Animal Medicinal Drug Use Clarification Act (AMDUCA) in 21 CFR 530.

Q: May a 503A pharmacy use bulk drug substances to compound for “office use” for veterinarians?

A: No. GFI #230 indicates that FDA would consider this a circumstance in which they would initiate regulatory enforcement against 503A pharmacies. GFI #230 tolerates compounding for “office use” using bulk substances only by 503B registered outsourcing facilities.

Q: If a pharmacy cannot purchase the FDA approved veterinary product to compound a prescription for an individual patient, can the pharmacy instead use a bulk drug substance to compound for animal patients?

A: No. If the FDA approved veterinary product will produce the desired clinical effect if used in a compound, it must be used as the starting ingredient.

Q: Can I compound using bulk drug substances in anticipation of compounded veterinary prescriptions that I have received in the past for that compound?

A: Yes. But only a maximum quantity of the compound dispensed for a 14 day consecutive period for the previous 6 months may be compounded in anticipation.

Q: Is it the pharmacist's or the veterinarian's responsibility to report adverse events associated with a compound prepared from bulk?

A: Both. GFI #230 requires the preparer of the compound (either the pharmacist or the veterinarian) to report any adverse drug events to FDA on Form 1932A within 15 days of occurrence.

Q: Can a 503B outsourcer compound anything that a veterinarian orders for office use?

A: No. 503B outsourcing facilities may only compound using bulk drug substances listed in Appendix A of GFI #230. The list of these bulk drug substances is being solicited from veterinary stakeholders and will be potentially compiled by an FDA Advisory Committee.

Q: If a veterinarian needs office use compounds for administration in the veterinary practice, what should they do?

A: The veterinarian should contact a 503B outsourcer to order the needed compounds.

Q: If I receive a prescription for a pet pig or chicken, may I use bulk drug substances to prepare the compound?

A: No. FDA clearly states in GFI #230 that all cows, pigs, chickens, turkeys, sheep, goats and non-ornamental fish (e.g. trout) are considered food-producing animals for which compounding with bulk drug substances is cause to initiate regulatory enforcement against the compounder.