



BETWEEN NECESSITY AND COMPLIANCE:

Understanding FDA's GFI #256 for Animal Drug Compounding



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The practice of compounding animal drugs using bulk drug substances¹ presents a challenging intersection of veterinary need and federal regulatory compliance. Governed by the Federal Food, Drug, and Cosmetic Act (“FDCA”), this area of animal healthcare has long operated in a legal gray zone,² with the FDA traditionally exercising discretion in

its enforcement. To bring clarity to this nuanced issue, the FDA issued Guidance for Industry #256 (“GFI #256”), which outlines the specific circumstances under which the agency will decline to take enforcement action against compounders of animal drugs using bulk drug substances.³ This article explores the practical implications of GFI #256

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for veterinarians and compounders, focusing on three critical requirements that must be met when compounding bulk drug substances for non-food-producing animals under a patient-specific prescription.⁴ By examining these key considerations, stakeholders can better navigate the complex regulatory landscape and ensure their practices align with FDA expectations.

Under the FDCA, an animal drug compounded using a bulk drug substance is a new animal drug.⁵ As such, the drug is required to undergo an approval or indexing process and is subject to other requirements of the FDCA, including labeling and good manufacturing practice requirements.⁶ Unfortunately, compounded drugs are not able to meet these requirements of the FDCA, and thus compounded animal drugs using bulk drug substances are generally prohibited under the FDCA.⁷

Nonetheless, the FDA has exercised discretion enforcing the FDCA against compounders of animal drugs using bulk drug substances.⁸ As a general rule, the FDA has refrained from enforcing the FDCA where there is no other medically appropriate treatment option for a patient.⁹

Recently, the FDA published GFI # 256 to formalize its enforcement discretion and clarify its thinking on the matter.¹⁰ Under GFI # 256, compounders of animal drugs using bulk drug substances benefit from the FDA's enforcement discretion if they can demonstrate the existence of certain required circumstances that depend on the type of animal being treated and whether there is a patient-specific prescription.¹¹ For example, where a bulk drug substance is compounded for a non-food-producing animal, and there is a patient-specific prescription, compounders are responsible for demonstrating eight elements, including the following:

- 01) Is the drug a copy of a marketed FDA-approved or indexed drug?
- 02) If the drug is a copy, is there a clinical difference between the drug and the FDA-approved or indexed drug as determined by the treating veterinarian?
- 03) If the drug has the same active moiety as an FDA-approved or indexed drug, is there a reason not to use the FDA-approved or indexed drug?¹²

Demonstrating the existence of these three elements is easier said than done. As such, the FDA has provided the following guidance in GFI # 256.

01)

Is the Drug a Copy of a Marketed Drug?

Before compounding a bulk drug substance for an animal drug for a non-food-producing animal pursuant to a patient-specific prescription, compounders must determine if they are compounding a copy of a marketed¹³ FDA-approved or indexed animal drug.¹⁴ Making this determination requires stakeholders to ask (i) if the drug has the same active ingredient or moiety¹⁵ as an FDA-approved or indexed drug and (ii)

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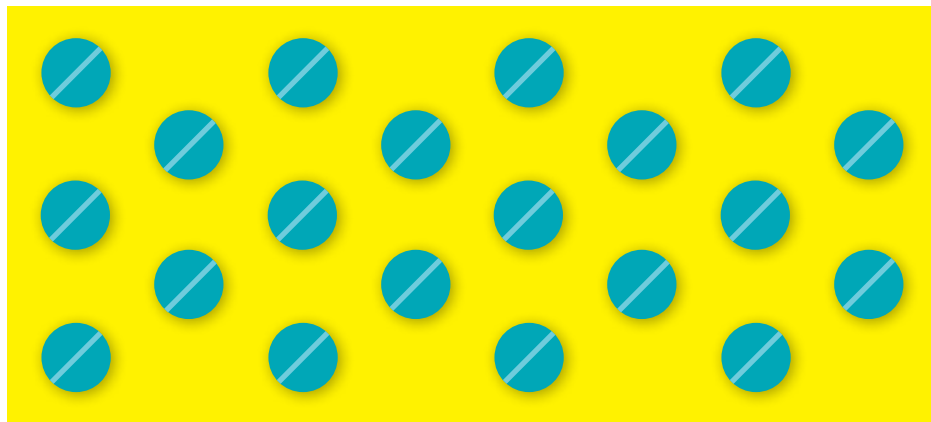
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whether the drug can be given by the same route of administration¹⁶ as the FDA-approved or indexed drug.¹⁷ If the answer to either question is “no,” the compounded animal drug is not a copy and can be compounded under the FDCA, as long as the other elements outlined in GFI # 256 are met.¹⁸

If the answer to both questions is “yes,” the drug is a copy and can be compounded only if (i) it produces a clinical difference compared to the FDA-approved or indexed drug as determined by a veterinarian and (ii) the other elements outlined in GFI # 256 are met.¹⁹



02)

Is There a Clinical Difference in the Copy?

If the animal drug being compounded is a copy, GFI # 256 requires that the treating and prescribing veterinarian determine and document that the copy produces a “clinical difference” in the treatment of the animal.²⁰ According to the FDA, “Clinical difference” encompasses a wide range of issues, including (i) formulation changes to exclude ingredients that are harmful to a patient, (ii) strength or concentration changes to accommodate variations in size, and (iii) changes in flavoring or dose to achieve patient compliance or to protect those administering drugs.²¹ A clinical difference does not include

variations in price (e.g., compounding to offer a less expensive product).²²

When compounding a copy of an FDA-approved or indexed drug, compounders must maintain a record of the veterinarian’s medical rationale that describes the clinical difference between the FDA-approved or indexed drug and the compounded copy.²³ This can be accomplished by retaining a copy of a prescription that includes the veterinarian’s explanation of the medical rationale or through a document maintained with the prescription.²⁴ If the prescribing veterinarian is responsible for compounding, the rationale should be noted in the patient’s medical record.²⁵

According to GFI # 256, the FDA generally does not intend to question a prescriber’s determinations that are documented in a prescription or notation.²⁶ The FDA focuses on whether (i) the compounder documents its determination and (ii) the documentation contains a medical rationale describing the clinical difference.²⁷

ACCEPTABLE BASIS TO COMPOUND A COPY

The FDA has provided compounders with several examples of acceptable notations for medical rationale that support the compounding of a copy of an FDA-approved or indexed animal drug.²⁸ According to the FDA, the notation should provide a brief statement of the medical rationale that contains the basic facts underlying the determination. Acceptable rationales include the following.²⁹

- **“PATIENT IS ALLERGIC TO INGREDIENT [X] IN APPROVED PRODUCT.”³⁰**
 - The FDA does not generally intend to question a veterinarian’s determination that a specific patient has an allergy to X. The allergy to X constitutes a medical rationale describing the clinical difference between the compound and approved product.³¹
 - The FDA indicates that identifying the specific allergenic ingredient (“X”) is an important part of the medical rationale because its presence in the approved product, and absence in the compounded product, produces the clinical difference in the patient.³²

- “[INGREDIENT NAME] IN APPROVED PRODUCT IS TOXIC TO THIS SPECIES.”³³
 - The FDA does not generally intend to question a veterinarian’s determination that an ingredient is toxic to a particular species and does not expect literature references or other information in the rationale.³⁴
 - The FDA will dispute this determination only in limited circumstances, e.g., if there is significant evidence to the contrary such as the presence of the specific ingredient in the same or greater concentration in FDA-approved products for that species.³⁵
- “PATIENT WOULD REQUIRE TOO MANY TABLETS OF THE APPROVED PRODUCT.”³⁶
 - The FDA does not generally intend to question a veterinarian’s determination that a patient will need to be administered an unreasonable number of tablets for the patient and, therefore, requires a prescription that significantly reduces the number of tablets administered.³⁷
- “PATIENT REQUIRES DOSE THAT WOULD REQUIRE A FRACTION OF THE APPROVED TABLET, AND TABLET IS NOT SCORED TO ACCOMPLISH THIS FRACTIONATED DOSE.”³⁸
 - The FDA does not generally intend to question a veterinarian’s determination that the patient will need to be administered a dose requiring a fraction of the approved tablet for the patient and the tablet is not scored to accomplish this fractionated dose. In this case, the prescription should be for a single, corresponding lower dose.³⁹
- “PATIENT CANNOT SAFELY BE PILLED WITH THE APPROVED CAPSULE.”⁴⁰
 - The FDA does not generally intend to question a veterinarian’s determination that a patient will not accept the specified dosage form if the prescription is for a different dosage form.⁴¹

The FDA generally does not intend to enforce the FDCA against persons compounding copies of FDA-approved or indexed animal drugs using bulk drug substances, as long as the prescribing veterinarian documents a clinical basis to compound the copy, and the other remaining elements outlined in GFI # 256 are documented to exist.

UNACCEPTABLE BASIS TO COMPOUND A COPY

The FDA provides several examples of unacceptable notations for medical rationale that fail to support the compounding of a copy of a marketed FDA-approved or indexed drug.⁴²

- “THE COMPOUNDED DRUG IS LESS EXPENSIVE.”⁴³
 - Economic consideration is not a medical rationale and will not be considered an acceptable reason for compounding a copy of an approved drug.⁴⁴
- “PREFER [COMPOUNDED DRUG/COMPOUNDER].”⁴⁵
 - The preferences of the prescriber or owner are not a medical rationale and will not be considered an acceptable reason for compounding a copy of an approved drug.⁴⁶
- “NEED HALF STRENGTH” (APPROVED PRODUCT IS 10 MG/ML SOLUTION, PRESCRIPTION IS WRITTEN FOR 10 ML DOSE OF 5 MG/ML SOLUTION)⁴⁷
 - The statement “need half strength” on its own is a conclusion and not a medical rationale describing the clinical difference. In this case, a prescription for a 5 ml dose of the 10 mg/ml approved product will deliver the same amount of active ingredient. The statement does not explain how the compounded product will produce a clinical difference in the individual patient. By contrast, a statement such as “need half strength to reduce irritation upon application” will explain the clinical difference and why a lower quantity of the approved drug cannot be used.⁴⁸

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The FDA intends to enforce the FDCA against compounders of copies of FDA-approved or indexed animal drugs where there is no documentation of a clinical difference between the compounded drug and the FDA-

approved or indexed animal drug. Economic considerations, preference, and conclusions are insufficient basis to compound a copy using bulk drug substances.

03) Is There a Reason Not to Use an FDA-Approved or Indexed Drug with the Same Active Moiety?

In the case where a compounded animal drug contains the same active ingredient moiety(ies) as an FDA-approved or indexed drug, a compounder is required to determine and document a reason that the FDA-approved or indexed drug cannot be used as the source of the active ingredient of the compound.⁴⁹ The FDA has provided several acceptable reasons to compound a drug with the same active ingredient moiety(ies) as an FDA-approved or indexed drug.⁵⁰

- **THE CHEMICAL PROPERTIES OF THE FDA-APPROVED OR INDEXED DRUG(S) PREVENT ITS PRACTICAL AND EFFECTIVE USE IN THE COMPOUNDING OF A SPECIFIC DRUG.⁵¹**
 - For example, it may not be possible to compound an ophthalmic solution from an approved topical cream, or it may not be possible to compound a sterile injectable from a non-sterile dosage form⁵²
- **AN INACTIVE INGREDIENT IN THE FDA-APPROVED OR INDEXED DRUG(S) IS TOXIC TO THE TARGET SPECIES AND CANNOT BE READILY SEPARATED.⁵³**
 - For example, a compounded drug is ordered for a dog, but the only drug product(s) containing that active moiety also contain the inactive ingredient xylitol, which is toxic to dogs⁵⁴
- **THE FDA-APPROVED OR INDEXED DRUG(S) THAT CONTAINS THAT ACTIVE MOIETY IS NOT AVAILABLE FOR COMPOUNDING.⁵⁵**
 - For example, a compounding pharmacy receives a prescription, but all drug products containing the active ingredient are only being sold directly to veterinarians by the sponsor(s)/distributor(s), and, therefore, the pharmacy is unable to purchase the products.⁵⁶

The FDA does not intend to enforce the FDCA against compounders of animal drugs making compounds with the same active ingredient as an FDA-approved or indexed drug, so long as the compounder documents a reason for not using the FDA-approved or indexed drug, and the other remaining elements outlined in GFI # 256 are shown to exist.



Conclusion

Under the FDCA, the decision to compound a bulk drug substance for an animal drug requires documentation that certain elements have been met. In the case of a non-food-producing animal with a patient-specific prescription, compounders are required to ask and answer several nuanced questions before compounding, including (i) whether the drug has the same active moiety or ingredient as an FDA-approved or indexed drug, (ii) whether the drug can be given through the same route of administration as the approved or indexed drug, (iii) whether the compound produces a clinical difference compared to the approved or indexed drug, and (iv) whether there is a documented reason not to use the approved or indexed drug. Absent appropriate documentation, compounders may violate the FDCA and be subject to enforcement for compounding animal drugs with bulk drug substances. Persons compounding animal drugs

using bulk drug substances for office stock, or for food-producing animals, need to consult GFI # 256, as the FDA requires the demonstration of a number of elements (not addressed in the article) for each of the compounding purposes.

References/Notes

1. FDA regulations define “bulk drug substance” 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 term does not include intermediates used in the synthesis of the substance. 21 CFR 207.1.
2. Sections 503A and 503B of the FDCA (21 U.S.C. §§ 353a, 353b), that provide certain statutory exemptions for compounded human drugs, do not apply to drugs compounded for use in animals.
3. HHS, FDA, CVM, Compounding Animal Drugs from Bulk Drug Substances Guidance for Industry # 256 (August 2022), available at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/cvm-gfi-256-compounding-animal-drugs-bulk-drug-substances> [herein called “GFI # 256”].
4. Where compounding for office stock, or for food-producing animals, compounders need to consult GFI # 256. The FDA applies different requirements for bulk drug substances compounded for office stock, or for food-producing animals.
5. GFI # 256.
6. Id.
7. Id. This article explores the limitations of using bulk drug substances to compound animal drugs. It does not address the use of approved, conditionally approved, or indexed animal drugs as the source of material for compounded animal drugs. The FDA has indicated that it does not intend to take enforcement action against compounders using approved, conditionally approved, or indexed animal drugs as the source material for compounded animal drugs.
8. Id.
9. Id.
10. GFI # 256.
11. Id.
12. Id.
13. A drug is considered “marketed” if the drug manufacturer is making and offering the drug for sale. For animal drugs that are temporarily in shortage, the FDA will apply its process for mitigating shortages. Actions may include working with drug manufacturers and others in the animal health industry, speeding up the animal drug review and approval process, encouraging sponsors of alternate products to increase production, or refraining from taking action against imports of foreign-approved versions of the drug product.
14. GFI # 256.
15. An active moiety is the molecule or ion that is responsible for the physiological or pharmacological action of a drug, i.e., what makes it work. See 21 CFR 314.3. A molecule does not have a different active moiety if it is an ester, salt, or noncovalent derivative (such as a complex, chelate, or clathrate) of a molecule in an FDA-approved or -indexed drug. For example, for the active ingredients erythromycin stearate, erythromycin ethylsuccinate, and erythromycin lactobionate, the active moiety is erythromycin.
16. A route of administration is the means by which a drug is given to a patient, i.e., by shot, pill, etc.
17. GFI # 256.
18. Id.
19. Id.
20. Id.
21. Id.
22. GFI # 256.
23. Id.
24. Id.
25. Id.
26. Id.
27. GFI # 256.
28. Id. It is not possible to offer exhaustive guidance about the types of changes that result in a clinical difference to an identified patient. Similarly, it is not possible to offer exhaustive guidance about the variety of applicable medical rationales.
29. Id.
30. Id.
31. Id.
32. GFI # 256.
33. Id.
34. Id.
35. Id.
36. Id.
37. GFI # 256.
38. Id.
39. Id.
40. Id.
41. Id.
42. GFI # 256.
43. Id.
44. Id.
45. Id.
46. Id.
47. GFI # 256.
48. Id.
49. Id.
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51. Id.
52. GFI # 256.
53. Id.
54. Id.
55. Id.
56. Id.



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