

Contains Nonbinding Recommendations

Compliance Policy Guide Sec. 615.115 Extralabel Use of Medicated Feeds for Minor Species

Guidance for FDA Staff

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Guidance for FDA Staff

This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA office responsible for this guidance as listed on the title page.

Introduction I.

This revised Compliance Policy Guide (CPG) is an update to the Compliance Policy Guide published in April 2001. The revised CPG represents the Agency’s current thinking on extralabel use of new animal drugs approved for use in or on animal feed (medicated feeds) (as defined in 21 CFR Sec. 558.3(b)(8)) for minor species (as defined in 21 CFR 516.3(b)). Minor species are defined by exclusion as animals other than cattle, horses, swine, chickens, turkeys, dogs and cats. The CPG is intended to provide guidance to the field concerning the Agency’s exercise of enforcement discretion with regard to the extralabel use of

over-the-counter (OTC) and veterinary feed directive (VFD) medicated feeds in minor species. It does not confer any rights for or on any person and does not operate to bind FDA or the public.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, they describe the agency's current thinking on various topics and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in agency guidances means that something is suggested or recommended, but not required.

Background II.

Prior to 1994, the Federal Food, Drug, and Cosmetic Act (the FD&C Act) did not permit the extralabel use of animal drugs, but the Agency exercised enforcement discretion regarding extralabel use of animal drugs provided certain criteria were met. These criteria were published in Compliance Policy Guide 7125.06 and were largely incorporated into the Animal Medicinal Drug Use Clarification Act of 1994 (AMDUCA). AMDUCA amended the FD&C Act to permit extralabel uses under certain conditions. The regulations promulgated pursuant to AMDUCA are codified at 21 CFR part 530.

AMDUCA does not permit extralabel use of medicated feeds. However, there are some minor species that cannot be practically medicated in any way other than through the use of medicated feeds. Furthermore, minor species such as fish and game birds have very few drugs approved for their use. In such situations, a veterinarian may determine that extralabel use of medicated feed is needed to prevent suffering and death in these minor species.

Before the implementation of AMDUCA, the Agency occasionally exercised enforcement discretion for the extralabel use of medicated feeds in minor species based on a medical need as long as the medicated feeds were formulated and labeled in accordance with their approved application. This enforcement discretion continued after AMDUCA because the law does not permit extralabel use of medicated feeds. The Agency is providing this guidance to our field personnel on how to address such extralabel use.

On January 1, 2017, a number of drugs used in feeds convert from OTC marketing status to VFD marketing status as a result of the recommendations provided in Guidance for Industry #213: New Animal Drugs and New Animal Drug Combination Products Administered in or on Medicated Feed or Drinking Water of Food-Producing Animals: Recommendations for Drug Sponsors for Voluntarily Aligning Product Use Conditions with GFI #209. This revised CPG provides additional guidance to our field personnel on how to address the extralabel use of OTC and VFD drugs in medicated feed for minor species.

Policy III.

A. Summary Statement

"Extralabel use" means actual use or intended use of a drug in an animal in a manner that is not in accordance with the approved labeling. This includes, but is not limited to, use in species not listed in the labeling, use for indications (disease or other conditions) not listed in the labeling, use at dosage

levels, frequencies, or routes of administration other than those stated in the labeling, and deviation from the labeled withdrawal time based on these different uses. (21 CFR § 530.3(a)).

AMDUCA amended section 512 of the FD&C Act to permit extralabel uses of drugs under certain conditions except in animal feed. 21 U.S.C. 360b(a)(4)(A). The extralabel use of a new animal drug in animal feed in a manner other than permitted by section 512 of the FD&C Act and FDA's implementing regulations results in the new animal drug being unsafe under section 512(a)(1) of the FD&C Act and adulterated under section 501(a)(5) of the FD&C Act. Because the FD&C Act does not permit extralabel use of drugs in animal feed, such use causes the medicated feed to be unsafe under section 512(a)(2) of the FD&C Act and adulterated within the meaning of section 501(a)(6) of the FD&C Act. The Agency may consider regulatory action when it finds such use or intended use.

However, when there are no approved treatment options available and the health of animals is threatened, and suffering or death would result from failure to treat the affected animals, extralabel use of medicated feed may be considered for treatment of minor species. Because of the need to have therapeutic options available for treatment of minor species, and to help ensure animal safety and human food safety, FDA is issuing this revised CPG to provide guidance to FDA staff with respect to factors to consider when determining whether to take enforcement action against a veterinarian, animal producer, feed manufacturer, and/or feed distributor for the extralabel use of OTC and VFD medicated feeds in minor species. In general, the Agency will not recommend or initiate enforcement action against the veterinarian, animal producer, feed mill, or other distributor when extralabel use is consistent with this document.

B. General Considerations

In the course of an inspection or other activity to investigate compliance, field personnel must look at the following to determine whether to recommend or initiate regulatory action against a veterinarian, animal producer, feed mill, or other distributor for the extralabel use of OTC and VFD medicated feeds in minor species. *All* of the following conditions must be present in order to consider enforcement discretion:

1. The medicated feed is used in an extralabel manner only with the express prior written recommendation (see section C. Veterinarian Considerations) and oversight of a licensed veterinarian within the context of a valid veterinarian-client-patient relationship as defined in 21 CFR 530.3(i), which says "A valid veterinarian-client-patient relationship is one in which:
 - a veterinarian has assumed the responsibility for making medical judgments regarding the health of (an) animal(s) and the need for medical treatment, and the client (the owner of the animal or animals or other caretaker) has agreed to follow the instructions of the veterinarian;
 - there is sufficient knowledge of the animal(s) by the veterinarian to initiate at least a general or preliminary diagnosis of the medical condition of the animal(s); and

- the practicing veterinarian is readily available for follow up in case of adverse reactions or failure of the regimen of therapy. Such a relationship can exist only when the veterinarian has recently seen and is personally acquainted with the keeping and care of the animal(s) by virtue of examination of the animal(s), and/or by medically appropriate and timely visits to the premises where the animal(s) are kept."
2. The medicated feed is used in an extralabel manner only for treatment of minor species as defined in the Code of Federal Regulations (21 CFR 516.3(b)). As previously stated, extralabel use under this revised CPG is limited to:
 - use in minor species not listed in the labeling,
 - use for indications (diseases or other conditions) not listed in the labeling, and
 - extension of the labeled withdrawal time (see section C. Veterinarian Considerations/General).
 3. The Type A medicated article is approved for use in or on animal feed and such feed is manufactured and labeled according to the approved labeling as described in 21 CFR part 558;
 4. Extralabel use of medicated feed in a food-producing minor species is limited to use in a minor species similar to the species for which the medicated feed is approved. Extralabel use of medicated feed for:
 - aquaculture is limited to medicated feeds approved for use in aquatic species;
 - avian species is limited to medicated feeds approved for use in avian species; and
 - mammalian species is limited to medicated feeds approved for use in mammalian species.
 5. Extralabel use of medicated feed is limited to a farmed or confined minor species. Use for the treatment of unconfined wildlife is not appropriate and thus is outside the scope of this CPG;
 6. Extralabel use is limited to therapeutic treatment when the health of an animal is threatened and suffering or death may result from failure to treat. It is unacceptable under any circumstances to use a medicated feed in an extralabel manner for improving rate of weight gain, feed efficiency, or other production purposes.
 7. The person, including veterinarians, animal producers, feed mill distributors, or other distributors, as applicable, has not promoted or advertised the medicated feed for an extralabel use. Such promotional activity is not appropriate because extralabel use of medicated feed is not legally permissible under the FD&C Act.

This CPG does not apply to the extralabel use of a new animal drug used in animal feed if the new animal drug in question is not approved by FDA for use in or on animal feed. Further, this CPG does not apply to medicated feeds which contain a drug or drug class that is specifically excluded by FDA from extralabel use. At this time, these specific exclusions include all drugs or drug classes prohibited for

extralabel use in animals (21 CFR 530.41). Please note that all of the drugs on the prohibited list are dosage form drugs, and none of the drugs or drug classes on the prohibited list has an approved application for use in medicated feed. FDA intends that all such drugs or drug classes be excluded from this CPG even if, at some point in the future, any become approved for use in medicated feed. Examples of such prohibited drugs or drug classes are fluoroquinolones, glycopeptides, and cephalosporin antimicrobials. FDA will update this CPG if it becomes necessary to exclude the extralabel use in minor species of additional drugs approved for use in medicated feed.

C. Veterinarian Considerations

General

In the course of an inspection or other activity to investigate compliance, in order to consider enforcement discretion in cases where a veterinarian is recommending or authorizing the extralabel use of an approved new animal drug in or on animal feed for use in a minor species, field personnel must also determine that, along with meeting all of the applicable conditions listed above in section B. *General Considerations*, the veterinarian has done all of the following:

1. Made a careful diagnosis and evaluation of the therapeutic indication for which the drug is to be used;
2. Made a determination within the context of a valid veterinarian-client-patient relationship that there is no approved new animal drug that (i) is labeled for such use, and (ii) contains the same active ingredient in the dosage form and concentration necessary for treatment; or, in cases where there is an approved new animal drug, the approved drug is clinically ineffective (see #7) for the use for which the medicated feed is intended;
3. Ascertained that there is no therapeutic dosage form that can be practically used under legal extralabel use;
4. Instituted procedures to ensure that the identity of treated animals is carefully maintained;
5. Established a withdrawal period that is substantially extended beyond that of the approved use (supported by appropriate scientific information) prior to marketing of milk, meat, eggs, or other edible products derived from the treated minor species, if applicable;
6. Taken appropriate measures to ensure that assigned timeframes for withdrawal are met and no unsafe drug residues occur in any food-producing animal subjected to extralabel treatment; and
7. Has reported any adverse reactions to FDA within 10 days of occurrence by visiting FDA's webpage entitled "How to Report Animal Drug Side Effects and Product Problems" at: <http://www.fda.gov/AnimalVeterinary/SafetyHealth/ReportaProblem/ucm055305.htm>. The veterinarian also should have reported treatments that were not clinically effective.

Over-The-Counter (OTC) Medicated Feed

In cases where a veterinarian is recommending the extralabel use of an OTC medicated feed for a minor species, in order to consider enforcement discretion field personnel must determine that, along with meeting all of the applicable conditions listed above in sections *B. General Considerations* and *C. Veterinarian Considerations/General*, the veterinarian has done all of the following:

1. Made a written recommendation that includes the medical rationale (e.g., diagnosis, drug selection, dose and duration, and the required withdrawal period), dated within 6 months prior to use;
2. Provided the client with a copy of the written recommendation; and
3. Kept copies of the written recommendation and makes them available to the FDA upon request.

Veterinary Feed Directive (VFD) Medicated Feed

In cases where a veterinarian is authorizing the extralabel use of a VFD medicated feed for a minor species, in order to consider enforcement discretion field personnel must determine that, along with meeting all of the applicable conditions listed above in sections *B. General Considerations* and *C. Veterinarian Considerations/General* and satisfying the applicable requirements in the regulations relating to VFD drugs under 21 CFR 558.6, the veterinarian has done all of the following:

1. Completed a separate written recommendation to the client for the extralabel use that includes the medical rationale (e.g., diagnosis, drug selection, dose and duration, and the withdrawal period (see above at section *C. Veterinarian Considerations/General*), dated within 6 months prior to use;
 - a. Provided the client with a copy of the written recommendation; and
 - b. Kept copies of the written recommendation for 2 years and makes them available to the FDA upon request.
2. Completed the VFD consistent with the approved labeling for the indication. In the "Special Instructions" the veterinarian should note:
 - a. "This VFD is being issued in accordance with CPG 615.115";
 - b. The actual species for which the medicated feed is intended (unless that species is already reflected on the VFD because the VFD drug is approved for use in that minor species, but is being used for a different indication); and
 - c. The withdrawal time associated with the extralabel use if different than the labeled withdrawal time as already reflected on the VFD (see section *C. Veterinarian Considerations/General*).

D. Animal Producer (Client) Considerations

General

In the course of an inspection or other activity to investigate compliance, in order to consider enforcement discretion with respect to an animal producer using medicated feed in an extralabel

manner for a minor species, field personnel must determine that, along with meeting all of the applicable conditions listed above in section *B. General Considerations*, the animal producer has done all of the following:

1. Kept complete and accurate records of medicated feeds received, including labels, invoices, and dates fed. These records are kept for at least 2 years from the date of delivery of the medicated feed;
2. Instituted procedures to ensure that the identity of treated animals is carefully maintained;
3. Taken appropriate measures to ensure that assigned timeframes for withdrawal are met and no unsafe drug residues occur in edible products derived from an animal receiving extralabel treatment;
4. Used the medicated feed in accordance with Federal, State, and local environmental and occupational laws and regulations. This is especially important for aquaculture uses;
5. Met the requirements of the Federal Clean Water Act as implemented under the National Pollutant Discharge Elimination System (NPDES), as well as any requirements applicable to ground-water pollution. The producer should contact the offices responsible for issuing NPDES permits, and other similar permits, to be certain there are no objections to the use and release of the drug; and
6. Followed user safety provisions as set forth in approved product labeling to protect individuals who may be exposed to the drug.

Over-The-Counter (OTC) Medicated Feed

In cases where a veterinarian is authorizing the extralabel use of an OTC medicated feed for a minor species, in order to consider enforcement discretion, field personnel must determine that the animal producer has kept a copy of the veterinarian's written recommendation for the extralabel use of the medicated feed, the copy is being kept by the animal producer for at least 2 years after feeding the medicated feed, and during that time making it available to FDA upon request.

Veterinary Feed Directive (VFD) Medicated Feed

In cases where a veterinarian is authorizing the extralabel use of a VFD medicated feed for a minor species, in order to consider enforcement discretion, field personnel must determine that the animal producer has complied with the applicable VFD regulations in 21 CFR 558.6, including keeping a copy of the VFD for 2 years and during that time making such records available to FDA upon request.

E. Medicated Feed Manufacturer or Distributor Considerations

In the course of an inspection or other activity to investigate compliance, in order to consider enforcement discretion with respect to an individual or firm who manufactures and/or distributes medicated feed for extralabel use in minor species, field personnel must determine that the medicated feed manufacturer and/or distributor has done all of the following:

1. Formulated the medicated feed as approved¹;

¹The non-medicated ingredients (nutrients) may be customized to be appropriate for the diet of the minor species as long as the customization is not in conflict with the medicated feed approval. The manufacturer/distributor is expected to engage with the client (animal producer) and/or nutritionist to formulate a medicated feed with appropriate nutrient content for the minor species that is consistent with the terms of the approval.

2. Labeled the medicated feed to reflect the approved bluebird label (<http://www.fda.gov/AnimalVeterinary/Products/AnimalFoodFeeds/MedicatedFeed/BlueBirdLabels/default.htm>);
3. Maintained the manufacturing record (including capturing any nutrient modifications) for 1 year as required by 21 CFR part 225. (Note that any records that would also be required under 21 CFR part 507 relating to the manufacturing, processing, packing, or holding of animal food must be kept for at least 2 years); and
4. If applicable, met the requirements for the manufacture/distribution of a veterinary feed directive (VFD) medicated feed in 21 CFR 558.6, including maintaining the VFD for 2 years and during that time making such records available to FDA upon request.

IV. Regulatory Action Guidance

Divisions within the Office of Pharmaceutical Quality Operations (OPQO) should consult with CVM, Division of Compliance, prior to taking enforcement action against a veterinarian, animal producer, feed mill distributor, or other distributor for the extralabel use of OTC and VFD medicated feeds in minor species.

Priority for enforcement action for extralabel use will generally be given to:

1. Veterinarians who authorize such use of the medicated feed in a manner that is inconsistent with sections III. *B. General Considerations* and *C. Veterinarian Considerations*;
2. Animal producers who use the medicated feed in a manner that is inconsistent with sections III. *B. General Considerations* and *D. Animal Producer (Client) Considerations*; and
3. Individuals or firms that manufacture or distribute the medicated feed in a manner that is inconsistent with sections III. *B. General Considerations* and *E. Medicated Feed Manufacturer or Distributor Considerations*.

In cases where the circumstances described in sections III. *B.* through III. *E.* of this CPG do not exist, the following regulatory actions may be taken:

A Warning Letter is ordinarily the first choice of action. The following language should be used to cite the violation:

The animal drug **** is adulterated within the meaning of Section 501(a)(5) of the Federal Food, Drug, and Cosmetic Act [the FD&C Act] as its use or intended use does not conform to its approved application in accordance with Section 512(a)(1) of the FD&C Act.

The animal feed **** is adulterated within the meaning of Section 501(a)(6) of the FD&C Act as its use or intended use does not conform to its approved application in accordance with Section 512(a)(2)(A) of the FD&C Act.

If a veterinarian did not recommend or authorize the use of the medicated feed for extralabel purposes, the Warning Letter should be issued to the animal producer with a copy sent to the veterinarian, if applicable. If a veterinarian recommended the use of the medicated feed for extralabel use other than as described in section *III.C.*, the Warning Letter should be issued to the veterinarian with a copy sent to the animal producer.

If an individual or firm manufactures and/or distributes medicated feed other than as described in section *III.E.*, the Warning Letter should be issued to the manufacturer or distributor, with a copy to the animal producer and veterinarian, if applicable.

The medicated feed manufacturer or distributor also may be considered for enforcement action if there is sufficient evidence to show that it knew that the medicated feed was intended for extralabel use in other than a minor species.

If there is a tissue residue violation, the appropriate Division within OPQO should establish the responsible individuals. This would ordinarily be the animal producer and/or veterinarian. However, in rare situations, such as an incorrect formulation or use of a new animal drug that is not approved for use in medicated feed, the medicated feed manufacturer and/or distributor may be considered responsible for the violation. The appropriate Division within OPQO should follow Compliance Program Guidance Manual 7371.006 and should cite the tissue residue food adulteration violation under Section 402(a)(2)(C)(ii) of the FD&C Act.

Should field personnel have any questions about the application of this guide, they may call CVM's Division of Compliance at (240) 402-7001 or email at CVMcompliance@fda.hhs.gov.

V. Specimen Charges

Domestic Seizure

The animal drug **** is adulterated within the meaning of Section 501(a)(5) as its use or intended use does not conform to its approved application in accordance with Section 512(a)(1) of the FD&C Act.

The animal feed **** is adulterated within the meaning of Section 501(a)(6) as its use or intended use does not conform to its approved application in accordance with Section 512(a)(2)(A).

Material between asterisks is new or revised.

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