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Practices to Prevent Unsafe Contamination of Animal Feed from Drug Carryover

Guidance for Industry

Draft Guidance

This guidance document is being distributed for comment purposes only.

This guidance, when finalized, will replace Compliance Policy Guides Sec. 680.500 and 680.600.

Submit comments on this draft guidance by the date provided in the *Federal Register* notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with docket number FDA-2022-D-0173.

For further information regarding this document, contact Kevin Klommhaus, Center for Veterinary Medicine (HFV-236), Food and Drug Administration, 7519 Standish Place, Rockville MD 20855, 240-402-7001, email: CVMAnimalFoodPrograms@fda.hhs.gov.

Additional copies of this draft guidance document may be requested from the Policy and Regulations Staff (HFV-6), Center for Veterinary Medicine, Food and Drug Administration, 7500 Standish Place, Rockville MD 20855, and may be viewed on the Internet at https://www.fda.gov/animal-veterinary, https://www.fda.gov/regulatory-information/search-fda-guidance-documents, or https://www.regulations.gov.

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This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, we, or Agency) on this topic.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 staff responsible for this guidance as listed on the title page.

I. Introduction

This guidance describes practices available to medicated feed manufacturers to prevent unsafe contamination from drug carryover into a non-medicated animal feed or a different medicated feed. This guidance contains much of the information found in the Compliance Policy Guides Sec. 680.500 Unsafe Contamination of Animal Feed from Drug Carryover and 680.600 Sequencing as a Means to Prevent Unsafe Drug Contamination in the Production, Storage, and Distribution of Feeds (both of which we intend to withdraw after this guidance is finalized), but includes updates and additional information. For purposes of this guidance:

- "you" refers to those involved in the manufacturing and distribution of medicated feed.
- "manufacturing and distribution of medicated feed" refers to using equipment to manufacture, process, pack, hold, and distribute medicated feed, including, for example, storing, mixing, and conveying.
- "animal feed" or "feed" refers to animal food produced by medicated feed manufacturers. Such animal food may be referred to in this guidance as "medicated feed," or "non-medicated feed," depending on whether it is formulated to contain a new animal drug. For convenience, we refer to such new animal drugs as simply "drugs."
- "drug carryover" refers to the presence of a drug in a subsequent batch of animal feed.
- "unsafe contamination" of an animal feed refers to a degree of contamination, by a drug approved for a medicated feed use, that poses an unacceptable risk to human or animal health.

The contents of this document do not have the force and effect of law and are not meant to bind the public in any way, unless specifically incorporated into a contract. This document is intended only to provide clarity to the public regarding existing requirements under the law. FDA guidance documents, including this guidance, should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidance means that something is suggested or recommended, but not required.

II. Background

A. Drug carryover

Drug carryover generally occurs when a drug used in the manufacture of a batch of medicated feed, for which the drug is approved, gets inadvertently included in a subsequent batch of: (1) a non-medicated feed, (2) a different medicated feed for which the drug is not approved (e.g., medicated feed for another species), or (3) a medicated feed that contains the same drug that can result in a higher drug level than is stated on the labeling. Drug carryover can occur for various reasons, including, for example, the use of the same equipment to manufacture both medicated and non-medicated feed; the design, construction, or inadequate maintenance of feed manufacturing equipment; poor dust control in a feed mill; inadequate cleanout practices for manufacturing and distribution equipment between sequential batches of animal feed; or human error (Refs. 1 and 2).

Ideally, carryover of a drug from one batch to another should always be completely avoided. However, factors such as the use of shared equipment to manufacture various medicated and non-medicated feeds, and the design and performance of such equipment used for feed manufacturing may not allow for an absolute avoidance of all batch-to-batch drug carryover.

The current good manufacturing practice (CGMP) regulation for medicated feeds, found in 21 CFR part 225, contains requirements for the manufacturing, processing, packing, and holding of medicated feed. Some facilities, such as feed mills, are required to have a medicated feed mill license to manufacture certain medicated feeds (see 21 CFR 510.455(f), 21 CFR 558.4, and 21 CFR 558.5(g)). Section 21 CFR 225.1 applies to all medicated feed mills. Sections 21 CFR 225.10 through 225.115 apply to facilities that are required to hold an approved medicated feed mill license. Sections 21 CFR 225.120 through 225.202 apply to facilities that are not required to hold a license.

The CGMP regulation for medicated feeds requires that adequate procedures be established and used for all equipment used in the manufacture and distribution of medicated feed to avoid unsafe contamination of medicated and non-medicated feeds with drugs (see 21 CFR 225.65 and 225.165). Therefore, you should focus on preventing unsafe contamination of medicated and non-medicated feeds by minimizing or, if possible, avoiding drug carryover altogether.

Failure of a facility to comply with the requirements of the CGMP regulation for medicated feeds (21 CFR part 225), including failure to establish and follow adequate procedures for cleanout of equipment to avoid unsafe contamination of animal feed, causes medicated feed manufactured, processed, packed, or held at the facility to be adulterated under section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act). In addition, if the medicated feed you manufacture contains a drug that is not approved for use in that feed, the feed containing the drug may be considered unsafe within the meaning of section 512(a)(2) of the FD&C Act and adulterated under section 501(a)(6) of the FD&C Act.

When drug carryover from the manufacturing, processing, packing, or holding of medicated feed results in drug contamination of non-medicated feed, the contaminated animal feed is considered adulterated under section 402(a)(2)(C)(ii) of the FD&C Act.

For animal drugs used in food-producing animals, FDA establishes a tolerance for the drug residue in human food as part of the animal drug approval process (see 21 CFR 514.1(b)(7) and part 556). Drug residues detected in excess of an established drug tolerance in food derived from food-producing animals (e.g., edible animal tissues such as meat, milk, honey, or eggs), or any residues detected from a drug not approved for use in a food-producing animal, would result in that human food being adulterated under section 402(a)(2)(C)(ii) of the FD&C Act.

B. Additional regulations covering animal food

Additional regulations that may be applicable to your operations contain requirements intended to help ensure the safety of animal food.

The Current Good Manufacturing Practice, Hazard Analysis, and Risk-Based Preventive Controls for Food for Animals regulation, found in 21 CFR part 507, establishes requirements for baseline safety and sanitation standards (CGMPs) and hazard analysis and risk-based preventive controls for the manufacturing, processing, packing, and holding of animal food (which includes pet food, animal feed, and raw materials and ingredients). For guidance on CGMP requirements in 21 CFR part 507, see our Guidance for Industry (GFI) #235, "Current Good Manufacturing Practice Requirements for Food for Animals."[1] For our current thinking on the hazard analysis and risk-based preventive controls requirements in 21 CFR part 507, see our draft GFI #245, "Hazard Analysis and Risk-Based Preventive Controls for Food for Animals."[2] If you are subject to 21 CFR part 507, subparts A, C, D, E, and F (the animal food preventive controls requirements), and you have identified drug carryover as a hazard requiring a preventive control, you must follow the preventive control requirements in part 507. Compliance with the relevant requirements of part 507 is used to determine whether your facility's animal food is adulterated within the meaning of sections 402(a)(3) and (4) of the FD&C Act (see 21 CFR 507.1(a)).

The Sanitary Transportation of Human and Animal Food regulation is found in 21 CFR part 1, subpart O. In general, persons involved in the transportation of animal food, including medicated feed, must comply with the requirements as applicable. For information on this regulation, see our Small Entity Compliance Guide, "Sanitary Transportation of Human and Animal Food: What You Need to Know About the FDA Regulation."[3]

III. Practices to Prevent Unsafe Contamination from Drug Carryover to Protect Human and Animal Health

[1] https://www.fda.gov/media/97464/download

[2] https://www.fda.gov/media/110477/download

[3] https://www.fda.gov/media/108944/download

If you manufacture medicated feed for which an approved medicated feed mill license is required, you must ensure that all equipment that comes in contact with the active drug component, feeds in process, or finished medicated feed is subject to all reasonable and effective procedures to prevent unsafe contamination of manufactured feed (see 21 CFR 225.65(b)).

If you manufacture medicated feed for which an approved medicated feed mill license is not required, you must establish and use adequate procedures for all equipment used in the production and distribution of medicated feed to avoid unsafe contamination of medicated and non-medicated feeds (see 21 CFR 225.165).

If you manufacture medicated animal feed and you are subject to 21 CFR part 507, then the discussion below may suggest practices to use in your implementation of certain requirements of part 507.

Some factors you should consider when developing your practices to prevent unsafe contamination from drug carryover include:

- risks to human and/or animal health
- types of animal feed you manufacture (e.g., medicated, requiring a license)
- animal species
- production stages of the animals
- the drugs being used and their levels
- equipment used in your facility

As with all practices used to prevent unsafe contamination from drug carryover in animal feed, your cleanout practices should be designed to protect the health of the animals consuming the animal feed and, in the case of food-producing animals, protect human health. There are known health risks to animals from unsafe contamination of feed from drug carryover that you also should consider when developing your practices. Human health may be at risk if humans consume a product derived from animals that have consumed animal feed contaminated from drug carryover. To protect human health, it is important to minimize the potential exposure of food-producing animals (e.g., animals near slaughter, lactating dairy animals, and laying hens) to unsafe contamination from drug carryover.

Since every animal feed manufacturing system is unique, the steps you take to establish adequate practices to prevent unsafe contamination from drug carryover for your operations may be different from those appropriate for other facilities. You should ensure that all personnel involved in animal feed scheduling and production understand the practices you establish for your operations. You should have a plan for reevaluating your practices periodically to ensure that unsafe contamination from drug carryover does not occur.

The most commonly used practices are described below. Many animal feed manufacturers use a combination of these methods to suit the requirements of their manufacturing systems,

production schedules, and distribution equipment to prevent unsafe contamination from drug carryover and thus protect human and animal health.

A. Physical Cleanout

Physical cleanout of manufacturing and distribution equipment used to mix and handle animal feed is a practice that may include dry-type cleaning (e.g., vacuuming, sweeping, or scraping equipment used to make dry feed), or wet-type cleaning (e.g., washing equipment used to make liquid feed). Physical cleanout often can be effectively used on a single piece of equipment when physical cleanout of the entire system is impractical or may not be necessary to ensure animal feed safety. You should evaluate the entire production line when determining the pieces of equipment on which to perform physical cleanout. Physical cleanout is an important practice used to prevent unsafe contamination from drug carryover.

B. Flushing

Flushing is a practice that uses a predetermined volume of a non-medicated feed ingredient to help clean out residual drugs from the manufacturing line following a batch or lot of medicated feed to prevent unsafe contamination of subsequent batches of animal feed. The type and quantity of flush material and the frequency of flushing will vary depending on the facility, the types of medicated feed manufactured, and the capacity of the equipment based on the manufacturer's specification. Commonly, the amount of flush material used is 5-10% of the manufacturing equipment capacity. Corn, soybean meal, and peanut hulls often are used for this purpose due to their abrasiveness. If you manufacture medicated feeds for which an approved medicated feed mill license is required, the flush material must be properly identified, stored, and used in a manner to prevent unsafe contamination of other feeds (21 CFR 225.65(b)(2)). However, even if you are not subject to 21 CFR 225.65, we recommend you follow these procedures for your flush material to prevent unsafe contamination. When properly implemented, flushing can be an effective cleanout practice for equipment that is difficult to clean physically.

C. Sequencing

Sequencing is a preplanned order of production, storage, and distribution of different animal feeds designed to direct drug carryover into subsequent feeds that will not result in unsafe contamination. Sequencing should start with a clean system. When the same equipment is used, the greatest potential for drug carryover is in the first batch of animal feed manufactured following the manufacture of a batch of medicated feed. Therefore, sequencing helps ensure that any carryover into the next batch of animal feed you make after a medicated feed does not result in unsafe contamination. For sequencing to be effective, sequencing practices should be carefully planned and executed. Whenever sequencing is interrupted or not followed through as planned, cleanout practices, such as those described in sections III.A. *Physical Cleanout* and III.B. *Flushing*, should be considered.

The following list provides factors you should consider when designing your sequencing practice to prevent unsafe contamination from drug carryover and to protect human and animal health.

You should consider your specific manufacturing system when designing a sequencing practice. This is not an all-inclusive list.

- Animal feed for animals near slaughter, lactating dairy animals, or laying hens should not be manufactured and handled on the same equipment immediately following the manufacture of medicated feeds containing drugs requiring a withdrawal period or drugs not approved for use in those species and production classes, unless adequate cleanout practices are implemented.

- Animal feed that cannot contain a drug requiring a withdrawal period (e.g., feed intended for animals near slaughter, lactating dairy animals, or laying hens) should be manufactured first in the sequence. Medicated feed with the highest potential to cause unsafe contamination from drug carryover should be manufactured last in the sequence, followed by adequate cleanout of the system before restarting the manufacturing/processing/sequencing cycle.

- Manufacture of medicated feed containing drugs requiring withdrawal, such as Category II[4] drugs, may be followed by manufacture of animal feed intended for growing animals of the same species because such growing animals are far enough from slaughter that carryover drugs should be cleared from their tissues by the time of slaughter.

- Medicated feed containing drugs that could cause an unsafe residue in an animal's edible tissues if consumed by finishing animals should be manufactured after other animal feed. For example, non-medicated swine finishing feed should be manufactured before a medicated feed.

- When you are manufacturing multiple lots of medicated feed containing the same drug, the sequence should be scheduled to produce the feed containing the highest concentration of the drug first and feed containing the lowest concentration of the drug last. The feed with the lowest concentration of the drug in the sequence could then be followed by a non-medicated feed for the same species or a medicated feed containing that same drug for another species.

- Horses are particularly sensitive to ionophore drugs (e.g., monensin or lasalocid); ingestion of these drugs may result in severe or fatal effects in horses (Ref. 3). Horse feed should not be manufactured immediately after production of medicated feed containing an ionophore drug.

- Swine are sensitive to the interaction of the drug tiamulin with a polyether ionophore drug (e.g., narasin); the interaction could result in ionophore toxicity in swine (Ref. 4).

[4] Drugs approved for use in animal feed are placed into one of two categories: Category I or Category II. Category I drugs require no withdrawal period at the lowest use level in each major species for which they are approved (or are approved for use only in minor species). Category II drugs require a withdrawal period at their lowest approved use level for at least one major species, or are regulated on a "no-residue" basis or with a zero tolerance (21 CFR 558.3(b)).

To avoid this interaction, you should manufacture other animal feeds in between the manufacture of a feed containing a polyether ionophore and a swine feed containing tiamulin, or conduct a physical cleanout.

- Pre-ruminating calves are sensitive to salinomycin; ingestion of this drug may result in severe or fatal effects in pre-ruminating calves (Ref. 5). Pre-ruminating calf feed (e.g., milk replacer) should not be manufactured immediately after production of medicated feed containing salinomycin.

D. Other Equally Effective Practices

You may use alternative, equally effective practices to prevent unsafe contamination of animal feed from drug carryover other than those discussed in this guidance. We encourage you to contact the Center for Veterinary Medicine (CVM), Division of Animal Feeds at AskCVM@fda.hhs.gov to discuss alternatives to the practices presented in this guidance that you would like to use.

IV. References

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3. Matsuoka, T., et.al. 1996. "Review of Monensin in Horses." Journal of Equine Veterinary Science. Volume 16, Number 1: 8-15.

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5. Huyben, M.W.C., et.al. 2001. "Salinomycin poisoning in veal valves." The Veterinary Record. August 11, 2001: 183-184.