NOTE: The California Department of Food and Agriculture’s (CDFA) Safe Animal Feed Education Program (SAFE) guidance materials are provided for educational purposes only and do not guarantee adequacy of procedures or compliance with regulations.
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Introduction

Feed manufacturers are responsible for ensuring safety, quality, and purity of feed manufactured. Carryover occurs when feed from one batch remains in the manufacturing system and gets carried over into the subsequent batch of feed. Feeds which are formulated for a specific species and class of animal may include minerals, vitamins, or medication at a concentration that is not safe for a different species or class of animal. Furthermore, feeds that are formulated as a supplement or pre-mix may contain ingredients at a high concentration. Carryover of such feeds into the subsequent batch impacts purity of the product and may negatively impact animal health and/or food safety, including:

- toxicity to an animal drug,
- minerals, vitamins, or other additives at levels of toxicity, and
- drug residue in meat, milk, or eggs.

According to FDA Guidance for Industry # 272: “factors such as use of shared equipment…and design and performance of such equipment…may not allow for an absolute avoidance of all batch-to-batch…carryover.”1 Good manufacturing practices and effective cleanout procedures are used to avoid carryover. This guidance will provide information to help industry evaluate the risk for carryover, develop procedures to minimize the risk of carryover, and verify effectiveness of those procedures (Figure 1).

Figure 1. This guidance will aid industry to identify risk of carryover, develop cleanout procedures, and verify procedures are effective.
Definitions

- **Carryover**: Occurs when feed from one batch remains in the manufacturing system and gets carried over into the subsequent batch of feed. This occurrence often presents no risk to animal health or food safety. However, when certain ingredients are used in a formula risk of contamination, or “unsafe carryover”, into the subsequent feed may increase.

- **Species and class of animal**: Animal species are categorized by taxonomy and genus, and there are several production “classes” of animal within livestock species which have different nutrient demands and tolerances. For example, dairy cattle, beef cattle, and calves are the same species but different classes of animals and consume different diets.

- **FDA Drug Approval**: The use of animal drugs in feed is regulated by the United States Food and Drug Administration (FDA). The Code of Federal Regulations (CFR) Part 558, Subpart B, provides approved dosages for each species and production class of animal and indication of use.²

- **Type A Medicated Article**: “is intended solely for use in the manufacture of another Type A medicated article or a Type B or Type C medicated feed. It consists of a new animal drug(s), with or without a carrier or inactive ingredients (e.g., calcium carbonate, rice hull, corn, gluten)”.³

- **Type B Medicated Feed**: “is intended solely for the manufacture of other medicated feeds (Type B or Type C). It contains a substantial quantity of nutrients including vitamins and/or minerals and/or other nutritional ingredients in an amount not less than 25 percent of the weight. It is manufactured by diluting a Type A medicated article or another Type B medicated feed.”³

- **Type C Medicated Feed**: “is intended as the complete feed for the animal or may be fed "top dressed" (added on top of usual ration) on or offered "free-choice" (e.g., supplement) in conjunction with other animal feed. It contains a substantial quantity of nutrients including vitamins, minerals, and/or other nutritional ingredients. It is manufactured by diluting a Type A medicated article or a Type B medicated feed. A Type C medicated feed may be further diluted to produce another Type C medicated feed.”³

- **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.”³

- **Category II drugs**: “require a withdrawal period at the lowest use level for at least one major species for which they are approved or are regulated on a “no-residue” basis or with a zero tolerance because of carcinogenic concern regardless of whether a withdrawal period is required in any species.”³
A complete list of Category I and II drugs can be found the FDA CFR 558.4.4

- **A Veterinary Feed Directive (VFD) drug:** “is a drug intended for use in or on animal feed which is limited by an approved application...to use under the professional supervision of a licensed veterinarian. Use of animal feed bearing or containing a VFD drug must be authorized by a lawful veterinary feed directive.”3
  - A complete list of drugs can be found on the FDA website: https://www.fda.gov/animal-veterinary/development-approval-process/drugs-veterinary-feed-directive-vfd-marketing-status.5

- **Withdrawal Time:** The withdrawal time is the period following the last treatment with the drug during which the animal may not be offered for slaughter and during which products from this animal such as milk and eggs may not be offered for sale.19

- **Limitations for Use:** The CFR regulations often specify additional limitations for the use of the animal drug. Some examples of limitations for use found in the CFR regulations include but are not limited to:
  - “Not for use in laying chickens.”
  - “Do not feed to chickens over 16 weeks of age.”
  - “A withdrawal time has not been established for this product in preruminating calves. Do not use in calves to be processed for veal.”
  - “Do not feed to chickens producing eggs for human consumption.”
  - “This drug is not approved for use in female dairy cattle 20 months of age or older, including dry dairy cows. Use in these cattle may cause drug residues in milk and/or in calves born to these cows.”2

- **Flush, Flushing:** A practice that uses a predetermined volume of a non-medicated feed ingredient to clean out residual material from the manufacturing line following a batch or lot of feed to prevent unsafe contamination of subsequent batches of feed.1

- **Sequence, Sequencing:** The preplanned order of production, storage, and distribution of different feeds designed to direct carryover into subsequent feeds that will not result in unsafe contamination.1

- **Flush Verification:** The process of sampling and analyzing the first part of the next batch of feed following a cleanout procedure to verify the “flush” effectively removed carryover from the previous batch of feed. Despite the term, this process can be altered and applied to test each type of cleanout procedure for effectiveness.
Evaluate Risk of Unsafe Carryover

Before developing procedures to minimize unsafe carryover, feeds manufactured in the facility should be evaluated for risk of unsafe carryover. The risk of unsafe carryover increases if the feed mill manufactures for multiple species, various types of feed, medicated feed, and/or concentrated mineral supplements or pre-mixes (Figure 2). Cleanout procedures are used to counteract this risk and avoid unsafe carryover.

![Diagram showing the relationship between safe and unsafe carryover](image)

**Figure 2.** The risk of unsafe carryover must be balanced by adequate cleanout procedures which are verified as effective.

The following steps provide guidance in evaluating risk for unsafe carryover in a facility.

**A.** Identify all the following ingredients in use at the facility:

1. Each drug ingredient
   i. Type A Medicated Articles
   ii. Type B Medicated Feeds or Pre-mixes
   iii. Type C Medicated Feeds

2. Each other ingredient used at the facility which has potential to cause toxicity if consumed in excess
   i. Minerals
   ii. Vitamins
   iii. NPN
   iv. Other
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B. Identify species/classes of animals (for which feed is manufactured at the facility) that are sensitive to items identified in A. Including, but not limited to:

1. Sheep to copper (Table 2),
2. Poultry to sodium (Table 2),
3. Horses to ionophores (Table 1),
4. Selenium in all species,
5. Non-protein nitrogen in all species,
6. Milk and egg producing animals to VFD drugs (or any drugs not approved for use in those classes of animal),
7. Withdrawal periods of drugs in all species,
8. Any other species and classes for which the drugs in use at the facility are not approved for use or have limitations for use.

C. Evaluate risk of unsafe carryover considering the following;

1. Concentration of the drug or nutrient in feed formulations.
2. The potential for carryover in the specific equipment and conveyance system of the facility.
3. Variety of feed manufactured on common equipment such as:
   i. Pre-mixes to complete feeds,
   ii. Medicated to non-medicated feeds,
   iii. Feed for different species of animals.
Considerations to Avoid Drug Residue in Meat, Milk or Eggs

Administration of animal drugs in the proper dosage, method, and abidance of withdrawal times ensure no drug residue in the subsequent livestock products, such as meat, milk, or eggs. Every load of milk received at a processing plant is tested for drug residues under FDA’s National Drug Residue Milk Monitoring Program. FDA has established tolerance levels for antibiotics in milk including 10 parts per billion (ppb) for “sulfa” drugs and 30 ppb for chlortetracycline (CTC) and oxytetracycline, which are VFD drugs used in medicated feeds. There are no VFD drugs or other drugs with withdrawal periods approved for use in feed for female dairy cattle over 20 months of age, including dry dairy cows. Most VFD and withdrawal drugs are also not approved for use in feed for chickens, ducks or turkeys laying eggs for human consumption. The United States National Residue Program for Meat, Poultry and Egg Products monitors antibiotic residues in tissue and egg products.

Considerations for Judicious Use of Animal Drugs

Based on concerns regarding the development of antimicrobial resistant strains of bacteria, the FDA and the CDFA’s Antimicrobial Use and Stewardship Program (AUS) work to ensure the appropriate or judicious use of medically important antimicrobial drugs (MIAD) in food-producing animals. FDA Guidance for Industry # 209 states that judicious use of antimicrobial drugs means that unnecessary or inappropriate use should be avoided.

The FDA’s framework for appropriate or judicious use includes:

- “Limiting medically important antimicrobial drugs to uses in food-producing animals that are considered necessary for assuring animal health; and
- Limiting such drugs to uses in food-producing animals that include veterinary oversight or consultation.”

In addition to medically important antimicrobial drugs, development of resistance in any pathogen or parasite is a growing concern for the animal agriculture industry. Antiparasitic resistance is a concern recognized by the FDA, especially with feed-through antiparasitic drugs. There is also evidence of ionophore and coccidiostat resistance in microbe populations.
Considerations to Avoid Drug Toxicity

Drug toxicity resulting in illness or death can occur in animals for which the drug is approved for use and consumed in overdose. While error in formulation or feeding is the more likely reason for such mistakes, drug toxicity from carryover is a possibility that should be considered when manufacturing concentrated Type B medicated feeds. When multiple feeds medicated with the same type of animal drug are manufactured in sequence, the concentrations of each should be evaluated and the level of carryover tested to ensure that subsequent feeds do not contain more of the drug than is purported on the label.

Drug toxicity resulting in illness or death can also occur at very low levels of consumption in animals for which the drug is NOT approved for use. There are several animal drugs which have known adverse effects on certain species (Table 1). Since the drugs are not approved for use in those species toxicity is a result of inadvertent feeding. Extra caution to avoid carryover must be taken when a facility manufactures medicated feeds using these drugs and manufactures feeds for the species which may experience toxicity to the drug at low levels.
Table 1. Species-specific drug toxicity and adverse reaction considerations according to FDA CFR Part 558.2 Disclaimer: This table includes drugs approved for use in feed by the FDA, although some are rarely used in industry today. This table is not intended to be all-inclusive. Reference CFR 558 for drug approvals, warnings, and caution statements.

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Horses or Other Equine</th>
<th>Rabbits, Guinea Pigs, Hamster</th>
<th>Poultry</th>
<th>Swine</th>
<th>Ruminants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lincomycin</td>
<td>TOXIC</td>
<td>TOXIC</td>
<td>Approved; Chickens</td>
<td>Approved</td>
<td>TOXIC</td>
</tr>
<tr>
<td>Tilmicosin</td>
<td>TOXIC</td>
<td></td>
<td>Approved; Cattle</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tiamulin hydrogen fumarate</td>
<td>TOXIC</td>
<td></td>
<td>Approved**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laidlomycin propionate potassium</td>
<td>TOXIC</td>
<td></td>
<td>Approved; Cattle</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lasalocid</td>
<td>TOXIC</td>
<td>Approved; Rabbits</td>
<td>Approved; Chickens, Turkey</td>
<td>Approved; Cattle, Sheep</td>
<td></td>
</tr>
<tr>
<td>Lubabegron</td>
<td>TOXIC</td>
<td></td>
<td>Approved; Cattle</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monensin</td>
<td>TOXIC</td>
<td></td>
<td>Approved; Chickens, Turkey</td>
<td>Approved; Cattle, Goats</td>
<td></td>
</tr>
<tr>
<td>Narasin</td>
<td>TOXIC</td>
<td></td>
<td>Approved; Chickens</td>
<td>TOXIC to Mature Turkey</td>
<td></td>
</tr>
<tr>
<td>Salinomycin</td>
<td>TOXIC</td>
<td></td>
<td>Approved; Chickens, Game Birds</td>
<td>TOXIC to Mature Turkey</td>
<td>TOXIC to pre-ruminating calves</td>
</tr>
<tr>
<td>Semduramycin</td>
<td></td>
<td></td>
<td>Approved; Chickens</td>
<td>**</td>
<td></td>
</tr>
<tr>
<td>Zipilatorol Hydrochloride</td>
<td>TOXIC</td>
<td></td>
<td></td>
<td></td>
<td>Approved; Beef</td>
</tr>
</tbody>
</table>

** Swine being treated with tiamulin hydrogen fumarate should not have access to feeds containing residues of polyether ionophores (e.g., lasalocid, monensin, narasin, salinomycin, or semduramycin), as adverse reactions may occur.
Considerations to Avoid Toxicity from Minerals, Vitamins and Non-Protein Nitrogen

Minerals
Vitamins and minerals are both essential to animal nutrition and potentially toxic if consumed over a threshold. While presence of heavy metals such as lead, mercury or arsenic are avoided in animal diets, other minerals such as selenium must be added to diets to prevent deficiency in livestock. Both deficiency and toxicity can occur with most any mineral; however, certain minerals are more likely to cause toxicity. For example, sheep are very sensitive to copper and toxicity can occur if they consume a formula with adequate levels of copper for cattle.

There are five minerals identified as both a required nutrient for animals added to feed and ranked as “high” concern for animal health by the National Research Council (NRC): copper, selenium, molybdenum, sodium chloride, and sulfur (Table 2). Calcium, iron, phosphorous, potassium and zinc are categorized by “medium” concern for animal health by NRC (Table 3). These maximum tolerable limits in the total diet should be considered when developing sequencing and flushing protocols for concentrated mineral feeds.

Table 2. Maximum tolerable levels of minerals in the total diet (parts per million (ppm) or percent of dry matter (DM)) of 5 “high risk” minerals.

<table>
<thead>
<tr>
<th>Mineral</th>
<th>Poultry</th>
<th>Swine</th>
<th>Horse</th>
<th>Cattle</th>
<th>Sheep</th>
</tr>
</thead>
<tbody>
<tr>
<td>Copper (ppm)</td>
<td>250</td>
<td>250</td>
<td>250</td>
<td>40</td>
<td>15*</td>
</tr>
<tr>
<td>Selenium (ppm)</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Molybdenum (ppm)</td>
<td>100</td>
<td>150</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Sodium Chloride (% of DM)</td>
<td>1.7</td>
<td>3</td>
<td>6</td>
<td>4.5 growing animals, 3.0 lactating cows</td>
<td>4</td>
</tr>
<tr>
<td>Sulfur (% of DM)</td>
<td>0.4</td>
<td>0.4</td>
<td>0.5</td>
<td>0.3 high concentrate diet, 0.5 high forage diet</td>
<td>0.3 high concentrate diet, 0.5 high forage diet</td>
</tr>
</tbody>
</table>

* When their diets contain normal molybdenum (1–2 mg/kg DM) and sulfur (0.15–0.25 percent) concentrations.

Avoid unsafe carryover of minerals and vitamins by establishing effective flush and sequencing procedures to ensure carryover will not increase mineral or vitamin level of the subsequent feed to an unsafe level for that species.
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Table 3. Maximum tolerable levels of minerals in the total diet (parts per million (ppm) or percent of dry matter (DM)) of 5 “medium risk” minerals.

<table>
<thead>
<tr>
<th>Mineral</th>
<th>Poultry</th>
<th>Swine</th>
<th>Horse</th>
<th>Cattle</th>
<th>Sheep</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium (% of DM)</td>
<td>1.5 (growing), 5 (laying)</td>
<td>1</td>
<td>2</td>
<td>1.5</td>
<td>1.5</td>
</tr>
<tr>
<td>Iron (ppm)</td>
<td>500</td>
<td>3000</td>
<td>500</td>
<td>500</td>
<td>500</td>
</tr>
<tr>
<td>Phosphorous (% of DM)</td>
<td>1 (growing), 0.8 (laying)</td>
<td>1</td>
<td>1</td>
<td>0.7</td>
<td>0.6</td>
</tr>
<tr>
<td>Potassium (% of DM)</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Zinc (ppm)</td>
<td>500</td>
<td>1000</td>
<td>500</td>
<td>500</td>
<td>300</td>
</tr>
</tbody>
</table>

Vitamins
There is less research available regarding the tolerance of vitamins in livestock species; however, NRC has established “estimated upper safe limits” for vitamins A, D, and E (Table 4).

Table 4. Estimated upper safe limits in the total diet of vitamins by species of livestock (IU/ lb in diet).

<table>
<thead>
<tr>
<th>Vitamin</th>
<th>Chicken</th>
<th>Cattle</th>
<th>Horse</th>
<th>Sheep</th>
<th>Swine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin A</td>
<td>6,818 (growing), 18,181 (laying)</td>
<td>30,000</td>
<td>7,272</td>
<td>20,454</td>
<td>9,090 (growing), 18,181 (breeding)</td>
</tr>
<tr>
<td>Vitamin D3 (&lt; 60 days)</td>
<td>18,181</td>
<td>11,363</td>
<td>N/A</td>
<td>11,363</td>
<td>15,000</td>
</tr>
<tr>
<td>Vitamin D3 (&gt; 60 days)</td>
<td>1272</td>
<td>1,000</td>
<td>1,000</td>
<td>1,000</td>
<td>1,000</td>
</tr>
<tr>
<td>Vitamin E</td>
<td>454 (chicks)</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
</tbody>
</table>

* “Presumed upper safe level of about 75 IU/kg of bodyweight (BW)/day is suggested as a tentative guideline for safe dietary exposure to vitamin E. Because the dietary requirements of most species for vitamin E are in the range of 5 to 50 IU/kg of diet (or 2 to 4 IU/kg of BW/day), intakes of at least 20 times the nutritionally adequate levels should be well tolerated.”
Non-Protein Nitrogen

Another feed ingredient commonly used in commercial feeds which may pose feed safety risks if unintentionally present in non-target feeds or in excessive amounts is non-protein nitrogen sources, most commonly urea. Monogastric animals are not sensitive to urea; however, horses are more susceptible to toxicity than most. A dosage of 4g/kg of bodyweight can be lethal in horses. Urea toxicity is more prevalent in unacclimated ruminant animals, and dosage of 0.3 to 0.5 g/kg of bodyweight can cause adverse effects and 1- 1.5 g/kg of bodyweight is usually lethal\textsuperscript{14,15}. Ruminants may adapt over days or weeks to increasing amounts of NPN, but such adaptation is quickly lost in a few days. More information regarding the acceptable feeding level of non-protein nitrogen can be found in the California Code of Regulations (CCR)\textsuperscript{16} Sections 2790.7 and 2707, and the Association of American Feed Control Officials (AAFCO) Official Publication\textsuperscript{17}.

Develop a Plan to Minimize Carryover

After a thorough evaluation of ingredients for risk of unsafe carryover, the next step is to begin developing procedures to minimize the risk of such carryover from occurring. The practices used to adequately prevent unsafe contamination from carryover will vary for each unique facility. There is no regulated or scientific standard for the industry because each feed mill is unique in design, operation, and types of feed manufactured. The procedures used within a single facility may also vary depending on the relevant risk for each ingredient in use. For example, proper sequencing may reduce risk sufficiently for some ingredients of concern, while other ingredients may always prompt a flush along with proper sequencing. The procedures used to sufficiently reduce risk may also vary between different manufacturing lines in the same facility due to limitations of the equipment. Furthermore, some facilities may find the risk so high they decide to designate equipment specifically for manufacturing with a certain ingredient and not use that equipment for manufacturing other types of feed.

A comprehensive plan to minimize carryover should be developed for each:

- Ingredient identified as a potential risk for unsafe carryover.
- Manufacturing process, including:
  - Each mixer and/or different processing line
  - Storage bins
  - Transportation (truck compartment cleanout procedures)

The most common practices used to reduce carryover in industry are flushing and sequencing.
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**Flushing**

Flushing is a practice that uses a predetermined volume of a non-medicated feed ingredient to help clean out residual material from the manufacturing line following a batch or lot of feed to prevent unsafe contamination of subsequent batches of animal feed. Each facility must determine the appropriate type and quantity of flush material to use.

Consider all the following when developing flush procedures:

- Flush material must travel the same route as the ingredient of concern from the point of inclusion to conveyance, equipment, storage and load-out or sacking.
- Type of flush material(s) to use (consider texture).
- Quantity of flush material(s) to use.
  - Recommended flush amount is 5-10% of the mixer’s capacity (2-ton mixer = 400 lb).
- Time (seconds) flush material will be in the mixer before discharge.
- Multiple separate flushing procedures may need to be implemented for different manufacturing lines or types of feed.
  - Consider each manufacturing line or process individually.
  - Consider each type of feed manufactured individually.
- For one example of a flushing procedure see SAFE example Standard Operating Procedure (SOP) “Scheduling Sequence and Flushing SOP.”

A study completed at Kansas State University demonstrates the need to consider all above-mentioned items and develop flush procedures specific to the equipment and formula. They tested flush amounts at 2.5%, 5%, 10%, 15%, and 20% of mixer capacity after manufacturing a feed medicated with Nicarbazin at 113.5 g/ton. The results demonstrated that a larger flush amount did further reduce the degree of drug carryover. Sampling at the bucket elevator after flushing with 2.5% of mixer capacity resulted in 1.4 g/ton of Nicarbazin in the following feed; flushing with 5% of mixer capacity resulted in 1.0 g/ton; flushing with 10% of mixer capacity resulted in 0.8 g/ton; and flushing with 20% of mixer capacity resulted in 0 g/ton of Nicarbazin in the following feed. This study also demonstrated that drug carryover varied in certain sections of the equipment and conveyance. There was essentially no drug carryover in the following feed when sampled at the mixer or drag conveyor, and the greatest amount of carryover was found in the finished product bin. The location of drug carryover will likely vary between facilities depending on the type of equipment, conveyance, and load-out systems in use. When developing procedures, sampling at various points in the system may help to identify areas of residue hang-up at an individual facility.
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A second trial was conducted using monensin at 100 g/ton, 600 g/ton, and 1200 g/ton and flush amounts at 1.0%, 2.5%, and 5% of mixer capacity. This study demonstrated that a higher concentration of drug in the feed resulted in a greater amount of carryover. In the previous trial even the low flush amount of 2.5% of mixer capacity effectively minimized the carryover to 1.4 g/ton after manufacturing a feed containing 113.5 g/ton Nicarbazin. In this trial, the 100 g/ton monensin feed also effectively minimized carryover to 2-3 g/ton regardless of flush amount (1-5% of mixer capacity). However, the 600 g/ton monensin feed resulted in a carryover of 6-10 g/ton regardless of flush amount. Further, the 1,200 g/ton monensin feed resulted in a carryover of 12-15 g/ton monensin in the following non-target feed regardless of flush amount. In this case, flush amounts of less than 5% of mixer capacity were not effective at minimizing the monensin carryover of 600 and 1,200 g/ton monensin feeds. Unfortunately, this trial did not test the 600 g/ton and 1,200 g/ton monensin feeds with a flush amount of 10% or 20% of mixer capacity. However, results from the previous trial suggest that a greater flush amount would have been more effective.

Ultimately, this study supports the generally recommended flush amount of 10% of mixer capacity for effective flushing procedures. There is limited research regarding flushing and sequencing procedures. The degree of carryover varies greatly from facility to facility due to differences in equipment, conveyance, procedures, and types of feed manufactured. It is crucial to conduct in-house sampling and testing to ensure procedures are effective.

Sequencing

Sequencing is the preplanned order of production, storage, and distribution of different animal feeds designed to direct carryover into subsequent feeds that will not result in unsafe contamination. Other cleanout methods, such as flushing, should be used in conjunction with sequencing whenever sequence is interrupted or not followed. Proper execution of sequencing requires careful planning, which considers the following:

- Avoid manufacturing and handling medicated feeds for animals near slaughter, lactating dairy animals, and laying hens immediately following the manufacture and handling of a medicated feed containing a drug with a withdrawal period or drugs not approved for use in those species. It is recommended to manufacture feeds for these classes of animals FIRST in the sequence, and to generally manufacture non-medicated feeds prior to medicated feeds.

- Manufacturing of medicated feeds requiring a withdrawal may be followed by manufacture of feed for growing animals of the same species, because they are far enough away from slaughter that carryover drugs should be cleared from their tissues by the time of slaughter. When this does occur, sequence should place non-medicated supplements, premixes, or concentrates prior to complete feeds, as those products will be fed in smaller portions and further limit the potential for unsafe carryover.
Sequence medicated feeds to avoid unsafe drug carryover into subsequent unmedicated feeds, medicated feeds containing a different drug, or medicated feeds containing the same drug that may result in a level over the label guarantee. Methods to do so will vary depending on the facility, and may include:

- When manufacturing multiple lots of feed containing the same drug, begin sequence with highest concentration of drug and move to lowest concentration for that species BEFORE following with a non-medicated feed for the same species or a medicated feed containing the same drug for another species.\(^1\)

- Medicated feed with the highest potential to cause unsafe carryover is manufactured last in the sequence, followed by adequate cleanout of the system before restarting the sequence.\(^1\)

- A combination of both above techniques; Sequencing from highest concentration to lowest, and then back up to a feed with high potential to cause carryover, followed by an adequate cleanout of the system before restarting the sequence.

Feed for animals which have a known toxicity or sensitivity to a drug or mineral, or to a certain combination of drugs, should never be manufactured immediately followed a feed medicated with the drug(s) of concern. (See Table 1).

Sequence schedule should always be approved by a “Qualified Individual”, such as the Plant Manager or Lead Formulator.

See SAFE example “Scheduling Sequence and Flushing” SOP.

Other Cleanout Procedures

There are other procedures to effectively avoid carryover including, but not limited to, designated equipment and physical cleanout. Designating certain mixers, conveyance, storage bins, and trucks to the handling of feed associated with risk of unsafe carryover is an effective method to avoid unsafe carryover altogether. Facilities which handle prohibited mammalian proteins and manufacture feed for ruminants typically use this method to ensure there is no common equipment in use. If the facility has the capacity to designate equipment in such a way, the following considerations may help develop an effective plan to avoid carryover:

- Carryover has been shown to occur during storage and conveyance, not just within the mixer\(^18\). To effectively avoid carryover, the entire manufacturing system including storage and transport should be designated.
- Ensure design is easy to distinguish, employees are trained, and/or system is automated.
Other cleanout procedures may still need to be utilized if multiple types of feed are manufactured on the designated system. For example, within the designated system flushing and sequencing may still be necessary to avoid unsafe carryover of:

- Concentrated vitamins or minerals that may increase the level in the subsequent feed above that which is purported on the label.
- Medicated feed which may increase the level of medication in the next batch of feed (medicated with the same drug) above that which is purported on the label.
- Medicated feed into a subsequent batch of a feed that is medicated with a different animal drug.

Physical cleanout of the manufacturing system requires shut down of manufacturing and can be dangerous for employees, therefore is not typically utilized unless necessary. However, if manufacturing equipment shows buildup of material, then a physical cleanout should be performed. Build-up of material, especially in mixers which have oil, molasses, or other liquid products added, may cause equipment to perform differently and flush procedures that were effective previously to be ineffective. Any build-up of material observed in the manufacturing system is a cause for concern of unsafe carryover. Therefore, physical cleanout should be utilized occasionally, as needed, as part of the plan to minimize carryover.

Verify Procedures are Effective

The key to developing effective cleanout procedures is to support them with technical and/or scientific evidence such as sampling and testing to verify effectiveness of the flush. SAFE refers to this process as “Flush Verification” and works with industry to perform flush verification to ensure procedures are effectively minimizing carryover.

Flush Verification

A flush verification is performed by sampling and analyzing the first part of a feed next in sequence after the flush following manufacture of a medicated feed and/or any feed with an ingredient of concern. If the drug, mineral, or other ingredient marker is not found in the first part of the next batch of feed, the flush procedure was effective. The flush material is also sampled and tested to confirm it captured the residue of concern and quantify the level of carryover left in the system.

The following guidelines should be followed when performing a flush verification to determine effectiveness of flushing procedures:
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- Perform test using a formula with the HIGHEST concentration of the drug/mineral or other ingredient of concern used at the facility.

- Take a representative sample of the feed or perform a mixer efficiency test simultaneously with the flush verification to have a full picture of where the drug and/or mineral ended up. When flush verifications are found ineffective, SAFE has commonly found that the feed itself ended up being low in the medication or mineral of concern. This information helps problem solve.

- Perform a separate flush verification for each mixing and/or conveyance system at the facility.

- Perform a flush verification for each type of drug or other ingredient of concern used at the facility. For example, a separate flush verification should be performed for Selenium (over 600 ppm), a Category II VFD drug, and a Category I drug.

- Perform a test that is true to actual practices.

- Re-evaluate anytime there is a change in formulas, equipment, or procedures.

- See SAFE example “Flush Verification SOP” for steps to perform a verification.

- See SAFE example “Flush Verification Form” for a template to record results.

- Contact SAFE at safe@cdfa.ca.gov for help performing a flush verification.

Other Verification Activities

Although SAFE uses the term “Flush Verification” similar sampling and verification procedures can be used to determine the effectiveness of sequencing or other cleanout procedures. The key to verification activities is that they are conducted in a manner which is trying to find carryover. This includes performing the test on the most concentrated formula in use, then manufacturing a single batch of feed next in sequence and sampling the first part of the next batch of feed. This process should capture the “worst case scenario” for carryover to occur and provide a true test of effectiveness of the cleanout procedure.

A mixer efficiency study can be just as important as efforts to minimize unsafe carryover. If medicated or mineral feeds are not properly mixed, then concerns for toxicity are present within each batch of feed, regardless of carryover from other batches. See SAFE example “Mixer Efficiency” for steps to complete a mixer efficiency test, or contact SAFE for help in performing a mixer efficiency test.
Summary

Carryover in feed manufacturing has the potential to pose animal health and/or food safety concerns when certain ingredients are utilized including medicated feeds, concentrated minerals, concentrated vitamins, and non-protein nitrogen. The main concerns regarding animal health include animal drug toxicity in a species for which the drug is not FDA approved and inadvertent over-inclusion of drugs, minerals, vitamins, or other additives at levels of toxicity. The main concerns regarding food safety include inadvertent inclusion of medicated feeds which have limitations for use or withdrawal times which may result in drug residue in meat, milk, or eggs.

The following factors should be considered in developing procedures to prevent carryover:

- Assess the risk for unsafe carryover for:
  - Each ingredient in use at the facility which has potential for unsafe carryover.
  - Each species and production class of animal for which feed is manufactured.
  - The specific equipment and conveyance system of the facility.
  - Variety of feed manufactured on common equipment such as:
    - Premixes to complete feeds,
    - Medicated to non-medicated feeds,
- Use a combination of procedures to effectively avoid carryover, such as:
  - Flushing,
  - Scheduling sequence,
  - Designating equipment, and
  - Cleaning procedures.
- Perform verification activities to ensure procedures are effective.
- Perform employee training and implement record keeping to ensure procedures are conducted properly.
- Re-evaluate periodically and with any changes in formulations or equipment.

Examples of sequencing, flushing procedures, and flush verification procedures are provided as an example Prerequisite Program on the SAFE website under "Cleanout Procedures."


3) Code of Federal Regulations Title 21 Sec. 558.3. Definitions and general considerations applicable to this part. Link: [CFR - Code of Federal Regulations Title 21 (fda.gov)](https://www.fda.gov/regulatory-information/search-federal-register)


8) FDA Guidance for Industry # 209. The Judicious Use of Medically Important Antimicrobial Drugs in Food-Producing Animals. Link: [CVM GFI #209 The Judicious Use of Medically Important Antimicrobial Drugs in Food-Producing Animals | FDA](https://www.fda.gov/animal-veterinary/guidance-documents/judicious-use-medically-important-antimicrobial-drugs)


