# TASC Meeting July 12, 2022



## Business Items

Call to Order

Roll Call / Introductions – Establish Quorum

Approve Meeting Minutes from October 22, 2021

**Vice Chair Election** 

**TASC Vacancies** 

# Proposed TASC Research Grant Process 2022 - 2023



TASC Research Grant Process

## Three phased approach

## The grants process will take

## one year.

The proposed launch date for a robust grant program is October 2022.

## **Three Phased Approach**

- October 2022- Request for Concept Proposals sent to the Public
  November 2022- SAFE Webinar for Proposal Authors
  December 2022- Concept Proposals Due to the SAFE Program
  January 2023- TASC Review and Recommend Projects to Phase II
  January 2023- Notification Letters Sent to Applicants
  Appeals Process Notation on RFP
- March 2023- Full Proposals Due

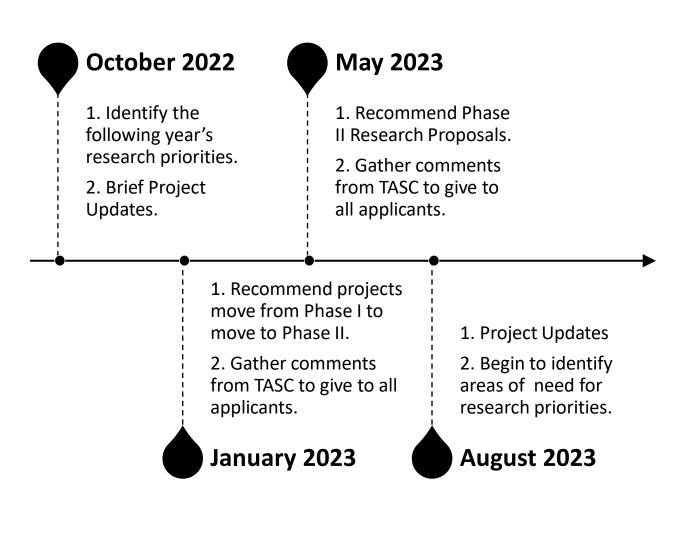
Phase I

Phase II

Phase II

- April 2023- Full Proposals Presented to TASC
- May 2023- TASC Review and Recommendation to FIAB
- June 2023- FIAB Recommendation to CDFA Secretary
- June 2023- CDFA Secretary Review and Final Approval Process Initiated
- August 2023- Notification Letters to Applicants of Status of Projects
- August 2023- Grant Agreement Paperwork Initiated
- November 2023- Research Begins

## TASC Annual Meeting Calendar



Drug and Mineral Carryover Technical Review

# Research Project Updates

## Goat Hemp Trial

## **Dairy Hemp Trial**

By-products Capacity Study

# Request for Proposal Ideas Discussion

### FEED AND LIVESTOCK DRUGS INSPECTION PROGRAM (FLDIP) TECHNICAL ADVISORY SUBCOMMITTEE (TASC)

California Department of Food and Agriculture (CDFA) WEB CONFERENCE MEETING

#### October 22, 2021 10:00 AM

#### MINUTES

#### TASC Members

Dr. Marit Arana, Chair John Martin Dr. Xixi Chen <u>CDFA Staff</u> Jenna Leal Rachelle Kennedy Cathryn McCandless KC Gutenberger Joshua Bingham **Interested Parties** 

Dr. Ed DePeters Dr. Katherine Swanson Maia Zack Joan Salwen Albert Strauss Vivianne Hay Dr. Breanna Roque

#### WELCOME AND INTRODUCTIONS

Dr. Marit Arana, Chair, called the meeting to order at 10:00 am. Self-introductions were made, and a quorum was established.

#### ASPARAGOPSIS FEEDING TRIAL FOR LACTATING DAIRY CATTLE

Joan Salwen of Blue Ocean Barns updated the TASC on the findings of the Asparagopsis Feeding Trial. Salwen stated the Asparagopsis was fed for 50 days on a commercial dairy farm. The goal of the study was to reduce emissions from lactating dairy cattle by 50%; the trial confirmed this hypothesis. Salwen noted the cattlemaintained milk quality and production during the trial. Salwen stated that lodine and Bromide levels were elevated due to the source of the Asparagopsis, as the product was harvested from the wild, which would be different than the product which would go to market. The product that Blue Ocean Barns is producing will be a seaweed digestive aid product grown under controlled conditions to eliminate the variability of lodine and Bromide in the final product.

Dr. Breanna Roque provided a synopsis of the feeding trial with results. Dr. Roque noted the feed needed to be slowly introduced to the cattle to improve dry matter intake and acceptance of the feed by the cattle. The Green Feed Machine was used to measure enteric methane emissions. Feed and milk quality were tested, and both were found to be within an acceptable and safe range for animal and human consumption. Methane emissions were measured throughout the trial per cow and over the experimental period. Dr. Roque stated the enteric methane emissions were decreased by over 50% of the baseline methane emissions.

John Martin asked if a Hazard Analysis was conducted on the Asparagopsis feed, specifically identifying any biological, physical, or chemical hazards that could impact animal or human health. Martin noted both CDFA and the feed industry would want a thorough Hazard Analysis conducted prior to the Asparagopsis going to the feed market. Both Iodine and Bromoform levels were identified during the trial discussion; Martin questioned how these potential hazards would be evaluated. Salwen responded that there is no current Hazard Analysis; however, Blue Ocean Barns would be willing to learn more about what that entailed and how to produce a Hazard Analysis.

Martin asked Albert Strauss if there were any concerns related to changes in the milk components associated with feeding Asparagopsis. Strauss did not offer any concerns regarding milk components that were evaluated and reported during the trial.

Dr. Xixi Chen had questions about the food safety perspective of feeding the Asparagopsis feed on a larger scale because the lodine levels were found to be elevated in the feed and milk. Dr. Chen questioned the use of the wild harvested seaweed with elevated levels of lodine versus a United States (US)-grown, lower-lodine Asparagopsis. Salwen stated the Asparagopsis that will be used going forward will be the same species of Asparagopsis and will not be grown in the open ocean that contains higher levels of lodine. The Asparagopsis that will be used in the future will be grown in controlled tank environments with much lower lodine levels.

Martin questioned if there could be a safety issue with mixing errors if elevated levels of Asparagopsis were inadvertently mixed into a batch of feed as the Asparagopsis is fed at such small levels of the overall diet. Strauss stated the Asparagopsis would need to be pelletized and added to the grain mix to ensure proper mixing on-farm.

Jenna Leal asked if Blue Ocean Barns had submitted a self-determination of Generally Recognized as Safe (GRAS) with the United States Food and Drug Administration (FDA). Salwen noted Blue Ocean Barns is looking for California specific approval and eventually federal approval of the feed. Discussion ensued with Salwen reiterating that Blue Ocean Barns would be submitting a self-determination of GRAS to CDFA.

Leal stated the trial outcomes give the Commercial Feed Regulatory Program (CFRP) good reason to be committed to further analysis and determinations in how to help move this feed product forward to the market. The CFRP will allow the TASC to consider the results of the trial and provide more time to examine the safety data of the Asparagopsis feed.

Dr. Chen stated that the American Association of Feed Control Officials feed approval route would be the preferred route for feed ingredient approval; however, it would take one to two years to go through the process. Dr. Chen recommended moving through the FDA's self-determination of GRAS process as well.

#### HEMP BY-PRODUCT FEEDING TRIAL FOR LACTATING DAIRY GOATS

Dr. Katherine Swanson updated the TASC on the status of the Goat Hemp By-product Feeding Trial. The hemp by-product residue was a coconut oil-soaked hemp product from which Cannabidiol (CBD) was extracted to produce CBD Oil. This hemp byproduct was then repurposed as a feed for lactating goats to assess the safety of feeding a hemp by-product to lactating animals and to assess whether the CBD would transfer into the blood, adipose, or milk that the goats produced. Dr. Swanson noted that the 20-day feeding trial had different treatment groups where goats were fed varying levels of the hemp by-product and that production records were also taken for each individual goat, including feed intake, milk output, and bodyweight. Dr. Swanson stated there were no differences in production between control and treatment fed groups; however, an acclimation period was necessary for goats to eat the hemp byproduct. Dr. Swanson reported both Milk Urea Nitrogen and Somatic Cell Counts dropped throughout the trial for the goats fed the treatment feeds.

Cannabinoids were found in blood and milk samples. Adipose sample data has not yet been received. Dr. Swanson stated there was elevated CBD found in treatment groups in the milk compared to the blood samples. Additionally, Tetrahydrocannabinol (THC) was found in both the blood and higher concentrations in the milk, despite the feed samples showing no evidence of THC at initial testing. Dr. Swanson hypothesized this may be accounted for by the sensitivity of the lab equipment which measured the THC in the feed compared to the more highly sensitive equipment which measured cannabinoids in the milk; however, this was an area of further research Dr. Swanson's lab will be exploring. According to Dr. Swanson, the cannabinoids are lipophilic compounds which were predictably more available in the milk compared to the blood.

Martin commented the study was well conducted considering the small number of goats in the trial.

Dr. Chen noted the study appears to be a pilot study which would provide a proof of concept for a larger study.

#### HEMP BY-PRODUCT FEEDING TRIAL FOR LACTATING DAIRY CATTLE

Dr. Swanson reported a dramatic increase in hemp by-product available for livestock feed since the legalization of Industrial Hemp as a legal crop; however, no current body of literature exists to identify what occurs to the animal and the milk produced by ruminant animals fed this hemp by-product. Dr. Swanson stated her previous research has been conducted on goats as a proof of concept and there is a paucity of research related to lactating dairy cattle fed any hemp by-product. Additionally, Dr. Swanson noted dairy cattle tend to have higher concentrations of fat in their milk compared to prior research conducted on goats as a ruminant model, which may lead to a greater accumulation of cannabinoids, CBD and THC in the milk from cattle fed this by-product.

Dr. Swanson stated the objective of the study would be to evaluate an ethanol extracted hemp by-product to determine if cannabinoids are found in the blood, adipose, and milk of lactating dairy cattle fed the by-product. The hemp by-product would be evaluated for

its nutritive qualities as well. The cannabinoids, heavy metals, and pesticides would be evaluated for safety in the feed samples. Milk, urine, adipose, and blood samples would all be collected to determine if cannabinoids from the hemp by-product are transferred to potential human food products such as adipose and milk.

Dr. Swanson stated that all milk produced from the feeding trial would be ineligible for sale into the human food market and would need to be discarded.

Martin questioned if there was a need for muscle tissue samples to be collected. Dr. Swanson stated this may be able to be added to the research protocol and she will further investigate muscle tissue sampling feasibility.

Dr. Chen stated this was an important study to be conducted and asked if it was likely to find cannabinoids in the milk of the lactating dairy cattle. Dr. Ed DePeters stated that the magnitude of cannabinoids may be greatly enhanced in dairy cattle fed hemp by-products. Discussion ensued.

Leal stated this research could help the CFRP provide information to the legislature when questions about the safety of hemp feed products arise.

**MOTION:** John Martin moved to recommend accepting this feeding trial to the Feed Inspection Advisory Board (FIAB) for full funding. Dr. Xixi Chen seconded the motion. The motion passed by present subcommittee members with a 3-0 vote, in favor of recommending the Hemp By-product Feeding Trial for Lactating Dairy Cattle to the FIAB for full funding.

#### CALIFORNIA BY-PRODUCT CAPACITY PLANNING RESEARCH PROPOSAL

Dr. DePeters presented a full proposal for a research project which aims to identify an inventory of California's by-product feedstuffs. The goals of the study are to identify the by-product feedstuffs produced in California by region and quantity produced, economic impact of the by-product production, and quantify the individual by-products fed to livestock by category of livestock.

Dr. DePeters noted that there is a limit to by-products that can be incorporated into the rations of livestock due to their nutritional limitations, seasonal challenges, and availability.

Martin stated that there is a lack of information of by-product capacity in California.

Dr. Chen stated this would be a benchmark study for California and would be a good fit for the current emphasis of the Safe Animal Feed Education program. Dr. Chen asked if there would be actionable steps provided to the industry for how to best use the data provided by this study. Discussion ensued.

Leal commented that the information procured from the study would provide baseline data. The data could then be used to advance more research on California's capacity to generate by-products for use in the California livestock feed industry. Discussion ensued.

**MOTION:** John Martin moved to recommend accepting the California Capacity Byproducts trial to the FIAB for full funding. Dr. Xixi Chen seconded the motion. The motion passed by present subcommittee members with a 3-0 vote, in favor of recommending the California Capacity By-products to the FIAB for fully proposed funding.

#### PUBLIC COMMENTS

No public comments were made.

#### **NEXT MEETING/AGENDA ITEMS**

The next meeting will be determined for a date between April and May 2022.

Future agenda items include:

- Hemp By-product Feeding Trial for Goats Conclusion and Publication Update
- Hemp By-product Feeding Trial for Cattle Update
- California By-product Capacity Planning Update
- Asparagopsis Feeding Trial and self-determination of GRAS status
- Camelina Revised Proposal
- Identify Areas of Research Need for 2023

#### ADJOURNMENT

**MOTION:** John Martin moved to adjourn the meeting; Dr. Xixi Chen seconded. The motion passed by present subcommittee members with a 3-0 vote.

The meeting was adjourned at 12:49pm.

Respectfully Submitted By:

#### ORIGINAL SIGNED BY JENNA LEAL

<u>10/22/2021</u> Date

Jenna Leal, Program Manager Feed and Livestock Drugs Program



**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.

### Summary

It is the responsibility of a feed manufacturer to ensure the safety of feed they are manufacturing. Carryover of animal drugs, minerals, or other ingredients into the subsequent non-target feed in the manufacturing sequence can be a known and reasonably foreseeable hazard in feed manufacturing. SAFE has developed this guidance to aid in understanding the hazards which carryover may present to both animals and humans. Good Manufacturing Practices should be implemented to ensure all medicated and non-medicated feeds meet quality and purity characteristics as purported.

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### **Background on Medicated Feeds**

The species and production class for which drugs are approved and the approved dosage for use in medicated feed are found in the United States Food and Drug Administration (FDA) Code of Federal Regulations (CFR) <u>Part 558</u>, Subpart B<sup>1</sup>.

#### **Definitions:**

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"<sup>2</sup>.

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."<sup>2</sup>

Refer to FDA CFR 558.4 for a complete list of Category I and Category II drugs<sup>3</sup>.



"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.<sup>2</sup>"

View complete list of drugs requiring a VFD on the FDA website at <u>https://www.fda.gov/animal-veterinary/development-approval-process/drugs-veterinary-feed-directive-vfd-marketing-status<sup>4</sup></u>.

#### Considerations for Drug Residue in Meat, Milk or Eggs

A "withdrawal period" is the time from when the animal was last treated with the drug to when the animal can be slaughtered for meat. Failure to administer animal drugs in the proper dosage, method, or abide by withdrawal times may result in drug residues in the meat. The withdrawal period for each drug used in medicated feed can be found within the FDA drug approval, and on the product label. In addition to a withdrawal period, each drug's approval regulates which production class, age, and/or weight of animals the approval applies to, and may have additional "LIMITATIONS FOR USE", regardless of withdrawal time, such as<sup>1</sup>:

- o "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 pre-ruminating calves. Do not use in calves to be processed for veal."
- o "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."

There are no VFD drugs or other withdrawal drugs approved for use in feed for female dairy cattle over 20 months of age, including dry dairy cows. Every load of milk received at a processing plant is tested for drug residues under FDA's <u>National Drug Residue</u> <u>Milk Monitoring Program.</u> 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<sup>5</sup>. 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<sup>6</sup>. It is important to review the FDA approvals, withdrawal, and limitations for use of all drugs in use at an individual facility.

#### Considerations for Drug Toxicity

There are several drugs which have known adverse toxic effects on certain species of animals **(Table 1).** Extra caution must be taken when a facility manufactures medicated



feeds using these drugs and manufactures feeds for species which may experience toxic reactions.

#### Special Consideration for Judicious Use of Animal Drugs

Based on concerns regarding the development of antimicrobial resistant strains of bacteria, the FDA and the CDFA <u>Antimicrobial Use and Stewardship Program (AUS)</u> work to ensure the appropriate or judicious use of medically important antimicrobial drugs in food-producing animals. <u>FDA Guidance for Industry # 209</u> 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 "1) limiting medically important antimicrobial drugs to uses in food-producing animals that are considered necessary for assuring animal health; and 2) limiting such drugs to uses in food-producing animals that include veterinary oversight or consultation"<sup>7</sup>. This warrants special consideration for carryover of medically important antimicrobial drugs.

In addition to medically important antimicrobial drugs, development of resistance in any pathogen or parasite is a growing concern for the animal agriculture industry. <u>Antiparasitic resistance</u> is a concern recognized by the FDA, especially with feed-through antiparasitic drugs<sup>8</sup>. There is also evidence of ionophore and coccidiostat resistance in microbe populations<sup>9,10</sup>. While this is not an immediate feed safety or human health concern, it is still an important consideration for the industry.

### **Drug Carryover Guidance**

Drug carryover occurs when a drug used in the manufacture of a batch of medicated feed, for which the drug is approved, is inadvertently included in the subsequent batch of:

- > a non-medicated feed,
- > a different medicated feed, or
- a medicated feed that contains the same drug that can result in a higher drug level than is stated on the label.<sup>20</sup>

There are two main reasons that carryover of medicated feeds may be a safety concern:

- > Drug residue in meat, milk or eggs (human health)
- Drug toxicity in certain species (animal health)

According to FDA Guidance for Industry # 272; "Ideally, carryover of a drug from one batch to another <u>should always be completely avoided</u>. However, 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 drug carryover"<sup>20</sup>. When developing practices to prevent unsafe drug carryover, individual facilities should consider risk to human and/or animal health, types of animal feed manufactured, animal species,



production stage of animals, the drugs being used and their levels, and equipment used in the facility<sup>20</sup>. Each individual firm must develop practices to prevent unsafe drug carryover specific to the facility and perform flush verification testing to ensure effectiveness. However, there is currently no guidance providing an acceptable level of carryover in determining effectiveness of flushing and/or sequencing procedures, when "zero" is not attainable. SAFE has reviewed FDA drug approvals and the limited scientific studies regarding drug carryover to develop the following tolerance for levels of carryover in results of flush verification testing:

- When there are toxicity implications of any drug for certain species carryover should not exceed ZERO g/ton if the feedmill manufactures feed for that species of concern (Table 1).
- Category II drug and/or VFD drug should not carry over into non-target feed more than 2 g/ton.
  - List of Category II Drugs.
  - List of VFD Drugs.
- When there is an FDA drug approval less than 20 g/ton in Category II or VFD feeds, carryover should not exceed 10% of the lowest drug approval (Table 2).
- Category I drug NOT requiring a VFD order should not carry over into nontarget feed more than 5 g/ton, or LESS in some cases (Table 3).

Two studies were conducted in dairy cattle which support the conclusion that feed contaminated with 1.8 g/ton CTC or Sulfamethazine for 21 days did not result in detectable levels of the drugs in milk<sup>11,12</sup>. However, due to a few VFD drug approvals that are very low (i.e., 2 g/ton), a tolerance for carryover of 2 g/ton is not acceptable for all VFD and Category II drugs. See **Table 2** for exceptions.

The carryover level of 5 g/ton for Category I drugs in non-target feeds (for species which do NOT have toxicity implications) is not a feed safety concern because most therapeutic drug approvals are above 10 g/ton, with few exceptions (i.e., diclazuril). The lowest approval for 'feed efficiency' purposes is about 4-5 g/ton, with few exceptions (bambermycin, efrotomycin). See **Table 3** for special considerations regarding low approvals and feed efficiency approvals of some Category 1 drugs.

Tables 2 and 3 also provide "Special Considerations" from the FDA CFR Part 558 which should be considered when developing sequencing and flushing procedures.



Table 1. Drug toxicity considerations of certain species according to FDA CFR Part 558<sup>1</sup>. Cleanout procedures should ensure there is <u>zero</u> drug carryover into feeds for the species of concern. *Disclaimer- this table is not intended to be all-inclusive and is not regulation- reference CFR 558 for drug approvals.* 

Drug Name	Species with Approval(s):	Toxicity Considerations
Lincomycin	Chickens, Swine	Rabbits, hamsters, guinea pigs, horses, or ruminants. Ingestion by these species may result in severe gastrointestinal effects.
Tilmicosin	Swine, Cattle	Horses or other equines.
Tiamulin hydrogen fumarate	Swine	Swine being treated with tiamulin should not have access to feeds containing residues of polyether ionophores (e.g., lasalocid, monensin, narasin, salinomycin, or semduramycin) as adverse reactions may occur.
Laidlomycin propionate potassium	Cattle	Horses or other equines.
Lasalocid	Chickens, Turkeys, Cattle, Sheep, Chukar, Rabbits	Horses or other equines.
Lubabegron	Cattle	Horses or other equines
Monensin	Chickens, Turkeys, Cattle, Bobwhite Quail, Goats	Horses or other equines, mature turkeys, guinea fowl. Ingestion of monensin by horses and guinea fowl has been fatal.
Narasin	Chickens, Swine	Adult turkeys, horses, or other equines. Ingestion of narasin by these species has been fatal.
Salinomyciin	Chickens, Game Birds	Adult turkeys, horses, and pre-ruminating calves <sup>20</sup>
Zilpaterol Hydrochloride	Beef	Horses or other equines.



Table 2. Special Considerations and Tolerances for VFD and Category II Drugs which have FDA CFR drug approval(s) below 20 g/ton. VFD and Category II drugs not listed should not exceed 2 g/ton of carryover. *Disclaimer- this table is not intended to be all-inclusive and is not regulation- reference CFR 558 for drug approvals.* 

Category II and/or VFD Drug	Lowest Drug Approval / Species	Species with Drug Approval in Medicated Feed	Special Considerations (FDA CFR Part 558)	Maximum tolerance of carryover in subsequent non-target feed.
Avilamycin (VFD)	13.6 g/ton / Chickens	Chickens, Swine	Not approved for swine over 14 weeks of age. Chickens must begin treatment on or before 18 days of age.	No more than 1.3 g/ton if manufacturing feed for chickens
Virginiamycin (VFD)	13.5 g/ton / Cattle	Chickens, Swine, Cattle	Not approved for layers or breeding cattle.	No more than 1.3 g/ton if manufacturing feed for cattle.
Hygromycin B (VFD)	8 g/ton Chickens, 12 g/ton Swine	Chickens, Swine	N/A	No more than 0.8 g/ton if manufacturing feed for chickens, and 1.2 g/ton if manufacturing feed for swine.
Lincomycin (VFD)	2 g/ton / Chickens	Chickens, Swine	Toxicity potential for rabbits, hamsters, guinea pigs, horses, or ruminants.	No more than 0.2 g/ton if manufacturing feed for chickens, ZERO if manufacturing feed for species with toxicity potential.
Tylosin (VFD)	8 g/ton Cattle	Swine, Cattle	N/A	No more than 0.8 g/ton if manufacturing feed for cattle.
Carbadox	10 g/ton / Swine	Swine	Not approved for pregnant swine or swine for breeding.	Not more than 1 g/ton.
Fenbendazole	14.5 g/ton /Turkeys	Zoo, Horse, Cattle, Turkey, Swine	Not approved for calves intended for veal, and not for dairy cattle if fed free choice.	Not more than 1.5 g/ton.
Halofuginone hydrobromide	1.36 g/ton /Turkeys	Chickens, turkeys	Not approved for layers.	Not more than 0.1 g/ton.
Ivermectin	1.8 g/ton / Swine	Swine	N/A	Not more than 0.1 g/ton
Maduramicin ammonium	4.54 g/ton / Chickens	Chickens	Not approved for layers.	Not more than 0.5 g/ton.
Zilpaterol Hydrochloride	6.8 g/ton / Cattle	Cattle	Not approved for breeding animals or calves intended for veal. Toxicity potential for horses.	Not more than 0.6 g/ton, and ZERO* if manufacturing feed for horses.

\*Is a beta-antagonist and therefore will also show up positive in drug testing of performance horses<sup>21</sup>.



# Table 3. Special Considerations and recommendations for Category I drug NOT requiring a VFD Order in which 5 g/ton of carryover may not be acceptable. *Disclaimer- this table is not intended to be all-inclusive and is not regulation-reference CFR 558 for drug approvals.*

Category I drugs NOT requiring a VFD.	Lowest Drug Approval / Species	Species with Drug Approval in Medicated Feed	Special Considerations (FDA CFR Part 558)	Maximum tolerance level of carryover in subsequent non-target feed.
Decoquinate	12.9 g/ton / Cattle	Chickens, Cattle, Sheep, Goats	Not approved for layers producing eggs for human consumption or cattle, sheep or goats producing milk for human consumption.	No more than 1.2 g/ton decoquinate if manufacturing feed for calves.
Lubabegron	1.25 g/ton	Cattle	Not for breeding animals, toxicity potential for horses.	No more than 0.1 g/ton
Melengestrol acetate	0.125 mg/lb of bodyweight	Cattle	Estrus suppressor	Consider productivity impacts of estrus suppression in breeding animals.
Monensin	5 g/ton / cattle (feed efficiency (FE))	Chickens, Turkeys, Cattle, Bobwhite Quail, Goats	Horses or other equines, mature turkeys, guinea fowl. Ingestion of monensin by horses and guinea fowl has been fatal.	Carryover should not meet or exceed approval for medicated feed.
Bacitracin methylene- disalicylate	4 g/ton / chickens (FE)	Chickens, Turkey, Swine, Cattle, Game Birds		Carryover should not meet or exceed approval for medicated feed.
Bacitracin zinc	4 g/ton / chickens (FE)	Chickens, Turkeys, Swine, Cattle		Carryover should not meet or exceed approval for medicated feed.
Bambermycins	1 g/ton / chickens (FE)	Chickens, Turkey, Swine, Cattle		Carryover should not meet or exceed approval for medicated feed.
Efrotomycin	3.6 g/ton / swine (FE)	Swine	Not approved for swine over 250 lbs.	Carryover should not meet or exceed approval for medicated feed.
Laidlomycin propionate potassium	5 g/ton / cattle (FE)	Cattle	Not approved for breeding animals. Toxicity potential in horses	Carryover should not meet or exceed approval for medicated feed.
Ractopamine	4.5 g/ton / swine (FE)	Swine, Cattle, Turkeys	Not approved for breeding animals	Carryover should not meet or exceed approval for medicated feed, and ZERO* if manufacturing feed for horses.

\*This is a beta-antagonist and therefore will also show up positive in drug testing of performance horses<sup>21</sup>.



### Mineral, Vitamin and Non-Protein Nitrogen Considerations

#### **Minerals**

It is well known that 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. There are six minerals identified as both a required nutrient for animals and ranked as "high" concern for animal health by the National Research Council (NRC): Copper, Flourine, Selenium, Molybdenum, Sodium Chloride, and Sulfur **(Table 4)**<sup>13</sup>. Boron, Calcium, Iron, Phosphorous, Potassium and Zinc are categorized by "medium" concern for animal health by NRC **(Table 5).** These <u>maximum</u> tolerable limits should be considered when developing sequencing and flushing protocols for concentrate mineral feeds.

Table 4. Maximum tolerable levels of minerals in the feed (parts per million (ppm) or percent of dry matter (DM)) of 6 "high risk" minerals which are added to feed by species of animal.

Mineral	Poultry	Swine	Horse	Cattle	Sheep
Copper (ppm)	250	250	250	40	15
Flourine (ppm)	150	150	40	40	60
Selenium (ppm)	3	4	5	5	5
Molybdenum (ppm)	100	150	5	5	5
Sodium Chloride (% of DM)	1.7	3	6	4.5 growing animals, 3.0 lactating cows	4
Sulfur (% of DM)	0.4	0.4	0.5	0.3 high concentrate	0.3 high
				diet, 0.5 high forage diet	concentrate diet, 0.5 high forage diet

Table 5. Maximum tolerable levels of minerals in the feed (parts per million (ppm) or percent of dry matter (DM)) of 6 "medium risk" minerals which are added to feed by species of animal.

Mineral	Poultry	Swine	Horse	Cattle	Sheep
Boron (ppm)	150	150	150	150	150
Calcium (% of DM)	1.5 growing birds, 5 laying hens	1	2	1.5	1.5
Iron (ppm)	500	3000	500	500	500
Phosphorous (%of DM)	1 growing birds, 0.8 laying hens	1	1	0.7	0.6
Potassium (% of DM)	1	1	1	2	2
Zinc (ppm)	500	1000	500	500	300



#### <u>Vitamins</u>

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 6)**<sup>14</sup>**.** 

Table 6. Estimated upper safe limits of vitamins by species of livestock (IU/ lb in
diet).

Vitamin	Chicken	Cattle	Horse	Sheep	Swine
Vitamin A	Growing 6,818	30,000	7,272	20,454	Growing
	Laying 18,181				9,090;
					Breeding
					18,181
Vitamin D3	18,181 <60	11,363 <60	1,000 >60	11,363	15,000 <60
	days; 1272 >60	days; 1,000	days	<60	days; 1,000
	days	>60 days		days;	> 60 days
				1,000	
				>60 days	
Vitamin E	454 (chicks)	*	*	*	*

\* "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 is non-protein nitrogen sources, most commonly urea. Urea is not very toxic to monogastric animals, but horses are more sensitive than other species and dosage of 4 g/kg of bodyweight can be lethal. Urea toxicity is more prevalent in 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<sup>15,16</sup>. More information regarding the acceptable feeding level of non-protein nitrogen can be found in the California Code of Regulations (CCR)<sup>17</sup> Sections 2790.7 and 2707, and the Association of American Feed Control Officials (AAFCO) Official Publication<sup>18</sup>.

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## SAFE Feed Manufacturing Carryover Guidance

#### **Procedures to Minimize Carryover**

The practices used to adequately prevent unsafe contamination from drug carryover will vary for each unique facility. It is important to support these practices and procedures with technical and/or scientific evidence, such as results of flush verification testing. The following factors should be considered in developing procedures to prevent drug carryover:

- Understanding the potential for carryover in the specific equipment and conveyance system of the facility
- Use a combination of procedures, such as;
  - Flushing
  - Scheduling sequence
  - Designating equipment
  - Cleaning procedures
- Variety of feed manufactured on common equipment, i.e;
  - Premixes to complete feeds
  - Medicated to non-medicated feeds
  - Multiple species of animals
- Employee training and understanding
- Re-evaluation periodically and with any changes.

The most common practices used to reduce drug carryover are flushing and sequencing. Examples of sequencing, flushing procedures, and flush verification procedures are provided as an example Prerequisite Program on the SAFE website under "Cleanout Procedures".

#### 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<sup>20</sup>. Each unique facility must determine the appropriate type and quantity of flush material to use and verify effectiveness through flush verification testing. Consider all of the following when determining procedures:

- > Type of flush material(s) (consider texture)
- Quantity of flush material(s)
  - Recommended flush amount is 5-10% of the mixer's capacity<sup>20</sup> (2-ton mixer = 400 lb.).
- > Time (seconds) flush material will be in the mixer before discharge.
- Consider all aspects of conveyance and equipment from the point of adding the drug or mineral, storage, to load-out or bagging



See SAFE example Standard Operating Procedure (SOP) "<u>Scheduling</u> <u>Sequence and Flushing SOP</u>".

#### Flush Verification:

A flush verification MUST be performed to determine that a flushing procedure is effective at removing the residue of concern. <u>SAFE is available to assist firms in</u> evaluating flushing procedures and testing for drug or mineral carryover.

- Perform test using a formula with the HIGHEST concentration of drug or mineral used at the facility.
- 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" and "Flush Verification Form".

A study completed at Kansas State University demonstrates the need to consider all above-mentioned items and perform flush verifications specific to the equipment and formula. They tested flush amounts of either 2.5%, 5%, 10%, 15%, and 20% of mixer capacity after manufacturing a feed medicated with Nicarbazin at 113.5 g/ton<sup>19</sup>. 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 performing a flush verification, sampling at various points in the system may help to identify areas of residue hang-up at an individual facility.

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<sup>19</sup>. This study demonstrated that a higher concentration of drug in the feed leads to 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 is going to vary greatly from facility to facility due to differences in equipment, conveyance, procedures, and types of feed manufactured. It is crucial to conduct in-house flush verification testing to ensure procedures are effective.

#### Sequencing:

Sequencing is the 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<sup>20</sup>. 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<sup>20</sup>.
- 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<sup>20</sup>. 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:

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- 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<sup>20</sup>.
- 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<sup>20</sup>.
- A combination of both of the 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 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 "<u>Scheduling Sequence and Flushing</u>" SOP.

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