PATHWAY TO MARKET USE OF NEW ANIMAL FEED INGREDIENTS

Cynthia Scholte
Center for Veterinary Medicine, U.S. Food and Drug Administration

Outline

- Regulation of substances intended for animal food
- Pre-market pathways for animal food
- Information to support a regulatory decision for animal food
  - Considerations for study design to support utility and safety
- Investigational food use authorizations

What is animal food?

- Animal food includes:
  - Livestock and poultry feed
  - Aquaculture feed
  - Pet food
  - Exotic animal food

Regulating Components of Animal Food

- Federal Food, Drug and Cosmetic Act
  - Basic food and drug law in the U.S.
  - Code of Federal Regulations (CFR) explains the requirements of laws
- Regulation of:
  - Animal drugs
  - Animal food and food additives
  - Color additives for animal food
- Intended use determines whether a substance is considered an animal food, drug, or color additive

Regulating Components of Animal Food

- Animal drug (e.g., medicated feed or water)
  - articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease
  - articles other than food intended to affect the structure or any function of the body of man or other animals

Regulating Components of Animal Food

- Food: articles used for food or drink for man or other animals
  - Provides taste, aroma, or nutritive value
- Food additive: articles intended to or that may be reasonably expected to become a component of food or affect the characteristics of food
  - Includes substances that may indirectly become a component of food through processing, packaging, etc.

Regulating Components of Animal Food

- GRAS substance: food substance that is generally recognized as safe (GRAS) for its intended use, either through scientific procedures or, for substances used in food before 1958, through experience based on common use in food

Regulating Components of Animal Food

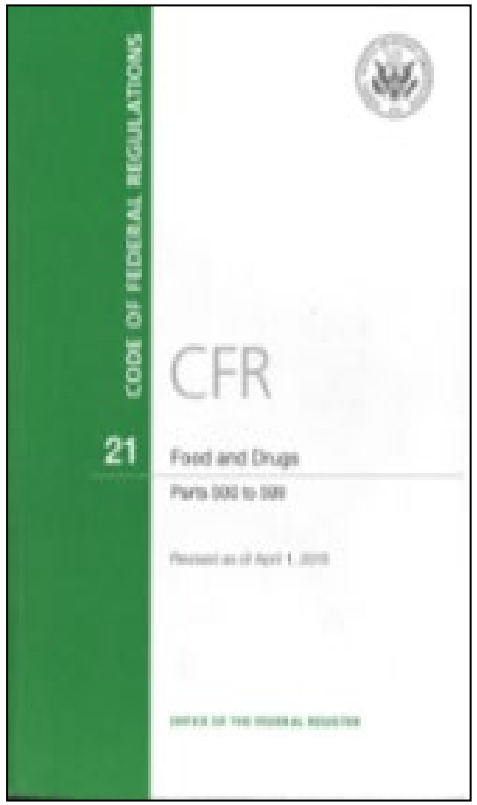
- Color additive: any dye, pigment or substance which when added or applied to a food is capable (alone or through reactions with other substances) of imparting color
  - Includes substances that, when fed to animals, impart color to meat, milk, or eggs

Regulating Components of Animal Food

- Note that the Dietary Supplement Health and Education Act (DSHEA) does not apply to animal food
  - 1996 Federal Register (FR) Notice 61:17706
  - Many supplements may be animal drugs based on their intended use

Pre-market Pathways

- Food Additive Regulation
  - 21 CFR 570 to 573
- Color Additive Regulation
  - 21 CFR 70 to 73
- GRAS Conclusion
  - 21 CFR 570.203 to 280



Pre-market Pathways

- Food additive regulation
  - Iterative process under food additive petition
  - Upon FDA's conclusion that the substance is safe and useful for its intended use, regulation published in CFR

Pre-market Pathways

- GRAS conclusion
  - An individual conclusion that the use of a substance is GRAS for an intended use
  - Based on safety evidence that is generally known and accepted by qualified experts
    - Same quantity and quality of information required as for a food additive, but safety evidence must be publicly available
  - Notifying FDA of GRAS conclusion is voluntary
  - FDA shares decision on a notified GRAS conclusion
    - Filed notice and FDA's response letter are posted to the Animal Food GRAS Notices Inventory website

Pre-market Pathways

- Color additive regulation
  - For color imparted by synthetic sources, as well as from sources of plants, minerals, algae, or animals
  - Iterative process under color additive petition
  - CVM provides scientific consultation on the safety of color additives intended for animal food
  - Upon FDA's conclusion that the substance is safe and useful for its intended use, regulation published in CFR

Potential Future Pre-market Pathways

- Innovative FEED Act
  - Proposed legislation requiring Congressional approval
  - Would establish zootechnical animal food substances as subcategory of food additives
  - Potential substance must:
    - Affect the byproducts of the digestive process
    - Alter the animal's gastrointestinal microbiome
    - Reduce the presence of foodborne pathogens of human health significance in animals intended to be used for food
  - Per February 2024 Letter to Industry, firms are encouraged to contact FDA early in the product development process

Potential Future Regulatory Process

- Animal Food Ingredient Consultation (AFIC)
  - Proposed in draft Guidance for Industry #294
  - Intended to provide an additional way for FDA to review ingredients and identify any safety concerns
  - FDA to share decision at completion of consultation
    - FDA's response letter to be posted to the AFIC inventory website

Supporting a Regulatory Decision

Depending on pathway, dossier for a substance intended for animal food will address:

- Intended use
  - Physical, nutritional or technical effect
  - Inclusion amount
  - Target animal
- Utility
  - Establishing the intended use
- Target animal safety
- Human food safety
- Environmental assessment
- Chemistry and manufacturing
  - Identity and composition
  - Analytical method validation
  - Specifications
  - Stability
  - Mixability
- Labeling
- Proposed regulation / ingredient definition

Study Design Considerations: General

- Scientifically sound experimental design
- Adequate sample size to achieve statistical power
  - Utility parameters: $P \leq 0.05$
  - Safety parameters: $P \leq 0.10$
- Conducted in animals representative of target animal species
- Appropriate endpoints and parameters
- Validated methods to analyze parameters

Study Design Considerations: Utility and Target Animal Safety

- Studies in support of **utility** must provide conclusive evidence that objectively demonstrate intended use of the substance in the intended animals
  - Studies should reflect use conditions in the US
  - Study duration should represent anticipated duration of use
  - Require a minimum of one adequate, well-controlled study
    - Number of study sites and study locations may differ for intended use of substance

- Studies in support of **target animal safety** must provide conclusive evidence that objectively demonstrate safety of the substance in the intended animals
  - Several experimental groups (e.g., control, 1X, 3X, 5X)
  - Study duration should represent anticipated maximum duration of use

Study Design Considerations: Human Food Safety

- Studies in support of **human food safety** must provide conclusive evidence that objectively demonstrate safety of the substance in the products intended for human consumption from the intended animals
  - Several experimental groups (e.g., control, 1X, 3X, 5X)
  - Study duration should address acute, sub-chronic, and chronic exposure
  - May require several study types (e.g., reproductive/developmental, genotoxicity battery)
    - Additional specialized or functional studies may be required (e.g., carcinogenicity, immunotoxicity, neurotoxicity, effects on human gut flora)
  - Studies should sample edible tissues to determine residues
    - Possible edible tissues: muscle, liver, kidney, fat or fat/skin, milk, eggs, honey

Study Design Considerations: Human Food Safety – Carcinogenicity

- Delaney clause - FDA cannot approve an article identified as a probable or known carcinogen to humans or animals, unless when given to animals, it does not result in residues in the human food
  - Must use a validated method that can reliably measure and confirm the presence of any residue of carcinogenic concern
  - Residue detection should be equal to or below the "no residue" level for the compound

Investigational Food Use Authorization

- Permits entry of edible products (e.g., meat, milk, eggs) from a specified number of animals to enter human food, and/or rendered material into animal food, during the investigational phase (prior to approval)
- Investigational studies may be performed without a food use authorization (FUA) if animal products are not going to enter the food supply
  - FUA is only required if investigational animals are intended to enter human or animal food
  - FUAs are intended for research that will support a future regulatory submission
- To request an investigational FUA:
  - If not previously established, submit request to establish an investigational food additive (IFA) file to animalfood-premarket@fda.hhs.gov
  - Provide information to support FUA request

Information to Support FUA Request

- Description of the investigational substance and its composition
- Narrative justifying request based on known safety of the substance
- Target animals, including species, class, age
- Number of animals from each species and class
  - Should reflect number of animals to be used in investigational study(ies)
  - Be specific; no more than the number of animals specified may be permitted

Information to Support FUA Request

Describe how the substance will be utilized in investigational studies:

- Form it will be fed
  - E.g., powder, liquid, pellets
- How it will be delivered
  - E.g., top-dress, mixed into a complete diet, sprayed onto feed
- Frequency and duration of feeding
  - E.g., once daily for up to 90 days
- Maximum amount be fed
  - Should reflect maximum amount, which may be above the intended use level
- Proposed minimum investigational withdrawal period
  - Time between when investigational substance is removed from diet and when edible tissues may enter human or animal food
  - Should be substantiated by information in submission
    - Request can be zero withdrawal period
    - If none requested and/or justification not provided, a longer more conservative period may be established

Information to Support FUA Request

- For substances that are a known or probable carcinogen:
  - Provide information in support of validated method
  - Provide information on residues from edible products (e.g., meat, milk, eggs) intended for human food that would be subject of the FUA
  - Provide information on how shorter duration studies can be used to address residue accumulation in edible tissues that would be seen in longer duration studies

Additional Information & Consultation

- Pre-submission Consultation
  - Encourage everyone to contact and meet with us early and often
  - GFI #262: Presubmission Consultation Process for Animal Food Additive Petitions or Generally Recognized as Safe Notices
- Protocol Review
  - Can submit protocol(s) for review and concurrence prior to a study being conducted
  - GFI #56: Protocol Development Guideline for Clinical Effectiveness and Target Animal Safety Trials
- Preparation of regulatory dossier
  - GFI #221 Recommendations for Preparation and Submission of Animal Food Additive Petitions
- Address Human Food Safety
  - GFI #3 General Principles for Evaluating the Human Food Safety of New Animal Drugs Used In Food
  - GFI #149 Studies to Evaluate the Safety of Residues of Veterinary Drugs in Human Food

animalfood-premarket@fda.hhs.gov


FDA
U.S. FOOD & DRUG
ADMINISTRATION