

#221

Guidance for Industry

Recommendations for Preparation and Submission of Animal Food Additive Petitions

Submit comments on this guidance at any time. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Room 1061, Rockville, MD 20852. Submit electronic comments on the guidance at <http://www.regulations.gov>. All written comments should be identified with the Docket No. FDA-2013-D-0928.

For further information regarding this document, contact [Mika Alewynse](mailto:Mika.Alewynse@fda.hhs.gov), Center for Veterinary Medicine, Division of Animal Feeds (HFV-229), Food and Drug Administration, 7519 Standish Place, Rockville, MD 20855, 240-402-5843; email: Mika.Alewynse@fda.hhs.gov.

Additional copies of this guidance document may be requested from the Policy and Regulations Staff (HFV-6), Center for Veterinary Medicine, Food and Drug Administration, 7519 Standish Place, Rockville, MD 20855, and may be viewed on the Internet at either <http://www.fda.gov/AnimalVeterinary/default.htm> or <http://www.regulations.gov>.

**U.S. Department of Health and Human Services
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Table of Contents

I. INTRODUCTION.....3

II. LEGAL AUTHORITY3

III. GENERAL CONSIDERATIONS AND THE FAP PROCESS.....4

A. Prior to Submitting a Petition.....4

B. Format and Information5

C. Identity and Composition6

D. Intended Use and Use Level, and Labeling.....10

E. Data Establishing the Intended Effect.....11

F. Analytical Methods.....12

G. Safety Evaluation.....12

H. Proposed Tolerances for the Food Additive15

I. Proposed Regulation15

J. Environmental Assessment.....15

IV. OTHER INFORMATION.....17

APPENDIX 118

Guidance for Industry
Recommendations for Preparation and Submission of
Animal Food Additive Petitions

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

I. INTRODUCTION

This guidance describes the types of information that the Food and Drug Administration's (FDA's) Center for Veterinary Medicine (CVM) recommends for inclusion in food additive petitions (FAPs) for food additives used in animal food. This guidance only applies to food additives for use in animal food. It is intended to help the petitioner (you) submit FAP information in a consistent and appropriate manner.

This guidance is intended to be used in conjunction with other CVM Guidance for Industry (GFI) documents that are cited throughout this document. Some of the referenced GFI documents pertain to animal drug products. These guidance documents are referenced because they provide information that is relevant to FDA's evaluation of the safety of food additives used in animal food. For example, FDA evaluates the human food safety of tissue residues present in edible tissues in a similar manner for new animal drugs intended for use in food-producing animals and for food additives used in foods for food-producing animals.

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

II. LEGAL AUTHORITY

FDA regulates foods and substances added to food under the Federal Food, Drug, and Cosmetic Act (FD&C Act). Many substances added to foods are food additives. Section 201(s) of the FD&C Act (21 U.S.C. § 321(s)) defines a "food additive" as "any substance the intended use of which results or may reasonably be expected to result, directly or indirectly, in its becoming a component of or otherwise affecting the characteristics of any food." Section 201(s) excludes from this definition any substance that is generally

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recognized as safe (GRAS) among qualified experts under the conditions of its intended use, or that qualifies for any of the other exemptions from the food additive definition (e.g., new animal drug, color additive, etc.).¹

Food additives require premarket approval based on data demonstrating safety. FDA issues food additive regulations specifying the conditions under which an additive has been demonstrated to be safe and, therefore, may be lawfully used. (See Section 409(a)(2) of the FD&C Act (21 U.S.C. § 348(a)(2)). A food that contains an unapproved food additive is deemed to be unsafe under section 409(a) of the FD&C Act and adulterated under section 402(a)(2)(C)(i) of the FD&C Act. Adulterated foods cannot be legally imported or marketed in the United States. Therefore, to use a food additive in animal food, FDA must issue a food additive regulation prescribing the conditions under which the additive may be safely used. Section 409(b) through (g) of the FD&C Act provides for a petition process to establish that a use of a food additive is safe.

Pursuant to Section 409(j) of the FD&C Act (21 U.S.C. § 348(j)), a food additive, or food containing a food additive, intended for investigational use may be exempt from the requirements of section 409 of the FD&C Act under the conditions set forth in Title 21 of the Code of Federal Regulations section 570.17.²

Under section 201(s) of the FD&C Act, the use of a food substance may be GRAS either through scientific procedures or, for a substance used in food before 1958, through either scientific procedures or experience based on common use in food. General recognition of safety through scientific procedures requires the same quantity and quality of scientific evidence as is needed for approval of an FAP (21 CFR 570.30(b)). The implementing regulations for eligibility for GRAS classification and affirmation of GRAS status for animal food are found at 21 CFR 570.30 and 21 CFR 570.35.

III. GENERAL CONSIDERATIONS AND THE FAP PROCESS

A. Prior to Submitting a Petition

Prior to submitting an FAP, CVM recommends that you verify that the substance you wish to use in animal food is not already approved as a food additive for your intended use. CVM publishes food additive regulations at 21 CFR parts 573 and 579.

¹ Under section 201(s) of the FD&C Act, the following types of substances are excluded from the food additive definition: (1) pesticide chemical residues in or on a raw agricultural commodity or processed food; (2) pesticide chemicals; (3) color additives; (4) substances used in accordance with a “prior sanction” (i.e., a sanction or approval granted prior to the enactment of the Food Additives Amendment of 1958 under the FD&C Act, the Poultry Products Inspection Act, or the Meat Inspection Act); (5) new animal drugs; and (6) dietary ingredients in or intended for use in a dietary supplement.

² The Code of Federal Regulations is available on the internet at <http://www.ecfr.gov/cgi-bin/ECFR?page=browse>.

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Furthermore, some substances that are GRAS for an intended use are listed in 21 CFR parts 582 and 584.

To be acceptable for a particular application, a food additive must meet the requirements (e.g., identity, specifications, and use limitations) set forth in 21 CFR part 571.

If you determine that you need to submit an FAP, CVM encourages pre-petition consultations, which could include requests for meetings or teleconference calls, to facilitate the development of information needed for an FAP, particularly for those that do not have previous experience preparing an FAP for animal food purposes. CVM also recommends that you initiate contact with CVM early in the process. A meeting or telephone conference with CVM staff to discuss a research plan for the proposed food additive is often useful. Once a research plan is developed, CVM strongly suggests that you submit protocols for CVM's review before initiating the studies.

Due to the wide variety of food additives and their intended uses, FDA cannot offer, in this guidance, detailed recommendations for some aspects of the FAP process. The FAP process is an iterative process and FDA offers detailed guidance to petitioners during the process. Such guidance depends on the type of food additive and its intended use. If your food additive involves the use of a specific technology (e.g., nanotechnology), CVM recommends you consult the FDA website for additional guidances pertaining to the application of that technology to products that fall under FDA's regulatory purview.³

If you need assistance determining the status of an animal food ingredient or preparing an FAP you should contact the Division of Animal Feeds in CVM in the following ways:

Mail:

Center for Veterinary Medicine,
Division of Animal Feeds,
7519 Standish Place, HFV-220,
Rockville, MD 20855

Phone: 240-402-7077

Fax: 240-453-6882

Email: Mika.Alewynse@fda.hhs.gov

B. Format and Information

Section 409(b)(2) of the FD&C Act (21 U.S.C. § 348(b)(2)) and FDA's implementing regulations at 21 CFR part 571 describe the FAP process and the information that must be submitted to FDA as part of an FAP. FDA reviews the submitted information and assesses whether, as a whole, the data and information demonstrate the safety of the food additive for an intended use as requested in the petition.

³ See guidances at <http://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

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The data and information in an FAP that are available for public disclosure are described in 21 CFR 571.1(h)(1). The data and information in an FAP that are not available for public disclosure are described in 21 CFR 571.1(h)(2). Food additive regulations are not proprietary, which means that any manufacturer that can produce the additive can sell the additive for the intended use.

Please note that, in addition to FDA's requirements, you should contact other Federal Government agencies such as the Occupational Health and Safety Administration (OSHA) and the Environmental Protection Agency (EPA) regarding actions that must be taken pursuant to other statutes prior to use of the food additive.

The general format required for an FAP, as outlined in 21 CFR 571.1(c), is as follows:

- Name and all pertinent information concerning the food additive, including chemical identity and composition of the additive or manufacturing methods and controls if the chemical identity and composition are not known;
- intended use, use level (amount of the food additive proposed for use), and labeling (cautions, warnings, shelf life, directions for use);
- data establishing the intended effect (physical, nutritional, or other technical effect);
- a description of analytical methods to determine the amount of the food additive in the food;
- safety evaluation;
- proposed tolerances for the food additive;
- proposed regulation; and
- environmental assessment.

C. Identity and Composition

1. Identity

This section of the FAP must include information which identifies and characterizes the food additive, including the composition of the food additive. For chemicals intended for use as food additives this information should include: (1) formal chemical name; (2) common names, synonyms, or trade names; (3) Chemical Abstracts Service (CAS) registry number; (4) empirical and structural formulae, and molecular or formula weights. Information characterizing the chemical, biological, and physical properties that can be used to identify the food additive must be submitted as well.

For a food additive that is a mixture of substances ("mixture"), the FAP should identify as many of the component substances ("components") in the mixture as needed to adequately define the composition of that food additive. The minimum amount of a component in a food additive that is a mixture, that may need to be identified as a component in the food additive is determined on a case-by-case basis. In addition, the FAP should provide the composition of each component in the mixture.

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Material balance calculations⁴ for the manufacturing process of the food additive should be provided.

For food additives of natural origin, additional information describing the source of the additive should be included in order to identify the additive. Additional information describing the source of food additives of natural origin can include the systematic name, genus and species, variability based on climate, or other geographical factors.

Because of the potential variability in the strength, purity, and quality of food additives of natural origin, more information may be needed to identify these food additives than may be needed for other food additives. In an FAP, the information used to identify a food additive of natural origin must be sufficient to ensure clarity about the identity of the food additive in the food additive regulation.

Food additives of natural origin can be similar to other food additives that are mixtures in that they may contain more than one component. For a food additive that is a mixture of components, information about the identities of the components and their presence and amounts in the mixture ensures consistency in the identity and composition of the food additive. Similarly, for a food additive of natural origin, the identity and composition of the food additive should be consistent.

Users of food additives expect food additives to be exactly what they are claimed to be in terms of identity. The level of detail needed to identify a food additive of natural origin depends on the nature of the food additive and is determined on a case-by-case basis.

In accordance with 21 CFR 571.1(c) A, where such information is not available, a statement as to the reasons why it is not available should be submitted.

FDA recommends that you include additional relevant information depending on the specific food additive. For example, the characterization for an enzyme should include the systematic name, enzyme source, enzymatic activity, substrate specificity, amino acid sequence, enzyme kinetics (temperature and pH), and structural modifications introduced chemically or genetically. Appendix 1 of this document provides additional guidance for additives that are produced by fermentation and/or biotechnological processes using cell culture, bioengineered microorganisms, or bioengineered plants. This guidance does not cover genetically engineered animals. For information about the regulation of genetically engineered animals, see FDA's GFI #187 entitled "Regulation of Genetically Engineered Animals Containing Heritable Recombinant DNA Constructs."¹

⁴ For the purposes of this guidance, "material balance calculation" means a mathematical comparison between the amounts of material inputs and the amounts of material outputs of a process system.

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2. Manufacturing methods and controls

a. Manufacturing process

When the chemical identity and composition of the food additive is not known, you must provide information in sufficient detail to permit the evaluation of the method of manufacture and the analytical controls used during the various stages of manufacturing, processing or packaging of the food additive (21 CFR 571.1(c)). In practice, an FAP will most likely be deficient without a full and complete description of the methods used in the manufacturing process of the food additive and FDA will request this information from any sponsor who does not supply it with the FAP. Accordingly, FDA recommends that you include this information in your FAP under all circumstances.

This section should contain a full description of the methods used in the manufacture and processing of the food additive. This description should provide sufficient detail to allow CVM to evaluate the ability of the process(es) to produce a consistent food additive with specified strength, purity, and quality. For example, a complete description should include: (1) a list of all solvents, catalysts, and reactive ingredients used; the quantities of these used; and the order of addition of these chemicals during production; (2) times, temperatures, and pH conditions for all steps in the manufacturing process; (3) identification of all manufacturing control points; and (4) identification of all analytical methods used to monitor chemical reactions during manufacture, including information that demonstrates that the methods perform within appropriate limits. If manufacture of the food additive calls for extraction, separation, and/or purification steps, the starting material should be adequately identified and all methods and materials used to extract, separate, and/or purify the food additive should be provided. You should also identify any alternative methods you may use in the manufacture of the food additive and provide as full a description as possible for the alternative methods.

A complete description of the packaging process of the food additive, including the containers used and the final product's labeling (see section D below) should be provided. Dependent on the identity of the food additive, the packaging operation should be validated, and both theoretical and actual packaging yields should be provided. If the food additive is to be further processed with other ingredients or carriers into an animal food premix or supplement, a complete description of the manufacturing process to accomplish this should be provided. Each ingredient and carrier should be described by its chemical name, appropriate analytical tests, and specifications. The final packaged additive should also be described by a set of appropriate tests and specifications. These data and information should be consistent with the information present in the additive's labeling.

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b. Batch preparation

When fermentation processes are used, all instructions for manufacturing batch preparations should be given. Appendix 1 provides additional guidance for additives produced by fermentation processes. This should include procedures for preparing and maintaining the working cell banks.

c. Specifications for chemical identity and purity

To ensure that a food additive is of consistent chemical identity and purity, the FAP should describe the final food additive by a set of chemical, physical, and/or biological properties and specifications prescribing the minimum content of the desired component(s) and identifying and limiting any reaction byproducts and other impurities. The food additive's specifications and their ranges should be based on analyses of three to five production batches. If it is not possible to base specifications and their ranges on analyses of production batches, then the food additive specifications can be based on analyses of a significant number of pilot production batches. The number of pilot production batches needed to determine the food additive specifications is based on the variability observed between the pilot production batches during manufacturing. Raw data and statistical analyses of the data should be submitted.

The specifications can include, for example, physical form, color, minimum content of the desired component, ash content, moisture content, maximum content of reaction byproducts, and limits for impurities and contaminants.

d. Food additive stability and mixability

The FAP must include stability data (21 CFR 571.1(c) A). Stability testing should be conducted under the intended conditions of use of the food additive over its anticipated lifetime. Data from stability studies should be submitted for three production batches. If using pilot batches in place of production batches, you should consult the Division of Animal Feeds regarding stability testing. The data should be fitted to a least squares regression, with the upper and lower 95% confidence limits shown. Where regression analysis is not possible, analysis of variance is an appropriate statistical analysis method. The analytical method used to determine stability should be validated in the different animal food types that the food additive is intended to be used. Stability should be demonstrated for the food additive as packaged alone (e.g., as a final product with diluents or carriers) and for the food additive mixed in a representative animal food matrix (e.g., complete food or vitamin or mineral premix) for the projected time the additive and the animal food containing the additive will be available for sale. If stability testing is to be performed on pelleted, canned, or liquid animal food, then the time and temperature for pelleting, canning, and liquid food conditions, respectively, should be provided in the FAP. If needed to ensure the identity, strength, quality, or purity, an expiration date must be proposed (21 CFR 571.1(c) A).

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Many food additives are added to animal food at concentrations in the parts per million or even parts per billion levels, and it is essential that these additives can be homogeneously mixed in the animal food. When necessary, the FAP should provide sufficient data and information to demonstrate that the additive can be homogeneously mixed in a representative food matrix, using mixing equipment that is readily available to a finished feed manufacturer. That information should include the coefficient of variation. The final concentration of the additive in the intended food matrix will determine the acceptable amount of variability.

D. Intended Use and Use Level, and Labeling

1. Intended use and use level

In accordance with 21 CFR 571.1(c) C, a petition must include data establishing that the food additive will have its intended physical or other technical effect or that it may reasonably be expected to become a component, or to affect the characteristics, directly or indirectly, of food and the amount necessary to accomplish this. This section of the FAP should include a discussion of the intended use and use level of the food additive. Such a discussion should include: (1) the type of animal food in which the additive will be used; (2) use level of the additive to be used in each type of animal food; (3) proposed maximum and typical use levels expressed as a concentration by weight; (4) a clear statement of the intended effect(s) of the additive; and (5) the species, age, and life stage of animals that will consume the food additive.

A food additive may have more than one intended effect. Some examples of intended effects of food additives include the following attributes: nutrient, aroma/flavor, taste, soluble or insoluble fiber, stabilization, emulsification, sequestration, preservation, anti-oxidant activity, anti-caking, or another technical effect. A list of terms that describe some physical or technical functional effects of types of food additives is provided in 21 CFR 170.3(o).

If the food additive is one for which a tolerance, of any kind, is required in order to ensure its safety, the proposed use level should be no higher than the minimum level required to accomplish the intended effect, even though safety data may support higher tolerance (21 CFR 571.1(c) B). In other words, for these food additives, the proposed use level is determined based on the minimum level required to accomplish the intended effect and not based on the maximum tolerance level.

We advise you to discuss the intended use of the food additive with CVM early in the development process. Contact information for the Division of Animal Feeds is provided in section III.A of this document.

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2. Labeling

As specified in 21 CFR 571.1(c) B, you are required to submit copies of the labeling proposed for the food additive. The labeling is required to be in compliance with 21 CFR part 501. You should consult with CVM regarding the appropriate content and format of the labeling. In general, a food additive label should include the following: 1) the product name or brand name; 2) description of the purpose including the types of animal food to which it can be added; 3) list of all ingredients, including inert compounds, listed by their common or usual name in descending order of predominance according to weight in the marketed product; 4) directions for use, including caution or warning statements; 5) the name and principal mailing address of the manufacturer or distributor; 6) product expiration statement (if needed based on the stability testing discussed previously); and 7) a declaration of net contents, which should appear in the bottom 30% of the label. The labeling is also required to include any other information deemed necessary by FDA to ensure that the food additive can be safely incorporated and used in animal food.

E. Data Establishing the Intended Effect

Data must be submitted to demonstrate that the food additive will have its intended effect and the amount of the food additive required to accomplish the intended effect (21 CFR 571.1(c) C). The number of studies and the detail and type of data required to demonstrate the intended effect will vary, depending upon the food additive and its intended use. To demonstrate the minimum level required to accomplish the intended effect, the intended use of the food additive should be evaluated at several levels above and below the proposed use level (for example, at half ($1/2x$) the intended use level, at the intended use level ($1x$), and at two times ($2x$) the intended use level). The functionality experiments should be carefully designed, taking into account the need for controls. Additionally, some food additives may have a technologically self-limiting use level; for example, where the food additive has a maximum concentration in animal food above which the food becomes unpalatable to the animal. In such a case, data are still needed to demonstrate the intended effect of the additive and documentation should be provided about the self-limiting use level. As the self-limiting use level depends on characteristics of the food additive, the documentation needed to describe the self-limiting use level will depend on those characteristics.

For general guidance on writing a study protocol to evaluate the intended use of the food additive, you are advised to consult FDA's GFI #215 entitled "Target Animal Safety and Effectiveness Protocol Development and Submission."ⁱⁱ Analytical methods used to determine the intended effect of a food additive should be validated to ensure that they measure the appropriate parameter. Validation parameters should include variables, such as matrix effects.

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For additional guidance on the types of information that you can use to demonstrate the intended effect of a food additive, we recommend that you consult FDA's GFI #53 entitled "Evaluation of the Utility of Food Additives in Diet Fed to Aquatic Animals."ⁱⁱⁱ Although some of the recommendations in GFI #53 pertain specifically to food additives for aquatic animals that are used at extremely low use levels, such as vitamins, many of the recommendations are generally applicable to other types of food additives.

F. Analytical Methods

The petition must include stability data, and, if the data indicate that it is needed to ensure the identity, strength, quality, or purity of the additive, the expiration date that will be employed (21 CFR 571.1(c) A). The stability data should include a detailed description of the method(s) used to determine the strength, purity, and quality of the food additive. All tests used to establish final food additive specifications should be validated with respect to correctness or be commonly accepted methods, i.e., methods published in the Official Methods of Analysis of the Association of Official Analytical Chemists, the Food Chemicals Codex, or the United States Pharmacopeia. Such analytical methods should be described in sufficient detail and specificity to permit CVM to assess the capabilities of the methods to determine the food additive's strength, purity, quantity, and quality as it is produced, after it is purified, in its marketed and packaged matrix, and in representative animal food. The methods proposed must be practical methods that can be performed routinely by trained laboratory personnel. For general guidance on validating an analytical method, you are advised to consult FDA's GFI #63 entitled "Validation of Analytical Procedures: Definition and Terminology VICH GL1"^{iv} and GFI #64 entitled "Validation of Analytical Procedures: Methodology: Final Guidance VICH GL2."^v

G. Safety Evaluation

As stated in 21 CFR 571.1(c) E, the safety evaluation section of the petition must include full reports of investigations with respect to the safety of the food additive. Typically, safety studies (non-clinical laboratory studies) are conducted in accordance with the Good Laboratory Practice (GLP) regulations (21 CFR part 58). The FAP must include a statement that a safety study was conducted in compliance with GLP regulations or, if the study was not conducted in compliance with the GLP regulations, a brief statement of the reason for the noncompliance (21 CFR 571.1(k)). You should explain what impact the lack of compliance with GLP regulations has on any conclusions in such reports regarding the food additive's safety.

1. Human food safety

The FAP is required to have scientific data necessary for demonstrating that the residues of the food additive are safe to humans consuming edible products of animals fed the food additive. See Section 409(c)(3)(A) of the FD&C Act. The three areas below should be addressed in the FAP when the additive is intended for use in a food-producing animal species. In certain cases, the types of studies described in this and the other referenced guidance documents will not be appropriate, such as when a food additive will be used

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only in food products for companion animals. We encourage you to contact CVM to discuss what types of safety information should be included for a particular food additive under the conditions of its intended use.

a. Toxicology

The toxicity to human consumers potentially associated with the use of a food additive can be assessed using a standard battery of toxicology tests. Each test is designed to examine a different toxicological endpoint. See FDA's GFI #3 entitled "General Principles for Evaluating the Safety of Compounds Used in Food-producing Animals."^{vi}

We also recommend that you consult FDA's GFI #149 entitled "Studies to Evaluate the Safety of Residues of Veterinary Drugs in Human Food: General Approach to Testing VICH GL33" for general toxicology study recommendations.^{vii} You should consult the referenced guidance documents if you plan to design and conduct genotoxicity studies,^{viii} carcinogenicity studies,^{ix} reproduction studies,^x repeat dose (90-day) toxicity studies,^{xi} developmental toxicity studies,^{xii} or repeat dose (chronic) toxicity studies.^{xiii} We may ask for additional toxicology testing as necessary to demonstrate that there is reasonable certainty of no harm with respect to potential residues in the edible tissues of animals that humans may consume.

b. Residue chemistry

We recommend that you consult FDA's GFI #3 entitled "General Principles for Evaluating the Safety of Compounds Used in Food-producing Animals."^{xiv} GFI #3 provides a description of suggested residue chemistry studies to determine the amount of the food additive or substances/components that could be produced in or added to human food products derived from animals consuming the food additive. GFI #3 also describes studies to characterize those residues. These studies could include specially designed assays to characterize the distribution and potential accumulation of food additive residues, including the parent molecule and its metabolites, in the different tissues of food-producing animals and in milk or eggs. You should consult the referenced guidance documents if you plan to design and conduct metabolism studies to determine the quantity and identify the nature of residues,^{xv} laboratory animal comparative metabolism studies,^{xvi} marker residue depletion studies to establish additive withdrawal periods,^{xvii} or validation of analytical methods used in residue depletion studies.^{xviii}

c. Microbial food safety

If the food additive possesses measurable antimicrobial activity, such as antibiotics used in distillers grains production, sufficient data should be submitted to determine whether the additive has any adverse impact on the emergence and development of antimicrobial resistance among food-borne pathogens and related commensal bacteria in the intestinal tract of animals consuming the food additive. In addition, the impact on human intestinal flora should be assessed for such food additives to determine whether a microbiological acceptable daily intake (ADI) should be established for the food additive. We

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recommend that you consult FDA's GFI #152 entitled "Evaluating the Safety of Antimicrobial New Animal Drugs with Regard to Their Microbiological Effects on Bacteria of Human Health Concern"^{xix} and FDA's GFI #159 entitled "Studies to Evaluate The Safety of Residues of Veterinary Drugs in Human Food: General Approach to Establish a Microbiological ADI."^{xx}

2. Target animal safety

The FAP will need to address the safety of the food additive under its intended conditions of use (21 CFR 571.1(c) E). In most cases, a study should be conducted in the proposed target animal species to demonstrate safety. Target animal safety studies should be conducted using the life stage and animal species for which the food additive will be marketed. In cases where the food additive is intended for multiple animal species or life stages, the food additive should be tested in the most sensitive life stage and/or species. You should use current scientific literature to identify the most sensitive life stage and/or species. Prior to initiating studies, you should consult with us to determine if your identification of the most sensitive life stage and/or species is acceptable.

Target animal safety studies should demonstrate the margin of safety for the intended use of the food additive. When designing safety studies in target animals, at least three inclusion levels (treatments) of the food additive should be used. In addition, a concurrent control group of test animals should be included in the study. Thus, the study design should include at least four experimental groups: a negative control, the maximum proposed use level (1X), and two multiples of this level [in most cases three times (3X) and five times (5X)] for a period of time in excess of the recommended maximum duration of use. However, alternative study designs can be considered where appropriate. Parameters for evaluation of safety in each group can include: clinical observations (e.g., of behavior, appearance, and eating patterns), blood analyses, mortality, weight gain, feed intake, and necropsy findings (gross and histopathologic abnormalities). We also recommend that you consult FDA's GFI #185 entitled "Target Animal Safety for Veterinary Pharmaceutical Products VICH GL43"^{xxi} for general target animal safety study recommendations. The number of animals used in a study to evaluate the safety of a food additive should be based on the expected variation in the parameters that will be measured, i.e., the study should have sufficient animal numbers such that the power of the study is adequate to ensure that any treatment-related effects can be detected.

CVM requests that you contact us early in protocol development in order to determine how target animal safety studies can be completed without terminal end points.

We recommend you discuss target animal safety study designs with CVM early in the development process and then submit study protocols for CVM review and concurrence prior to initiating any target animal safety studies. For general guidance for writing protocols, consult FDA's GFI #215 entitled "Target Animal Safety and Effectiveness Protocol Development and Submission."^{xxii}

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H. Proposed Tolerances for the Food Additive

Tolerances for food additives fed to animal species used for human food represent the maximum concentration of the additive permitted in edible tissues (for example, meat, milk, and eggs). Tolerances are established based upon residues of the food additive in edible tissues of food-producing animals that consumed the additive. Tolerances are intended to ensure that residues of food additives in edible tissues will have no harmful effects when consumed by people. The potential for establishment of a tolerance is a facet of the human food safety evaluation discussed earlier.

I. Proposed Regulation

We recommend that you provide a proposed regulation as part of your FAP. This section of the FAP should contain a draft food additive regulation in which you describe the conditions under which the additive can be safely used in animal food. The proposed regulation should contain information adequate to ensure safety of the additive under each and every condition of use to be permitted and should include any restrictions, such as animal species limitations, that are important to ensure safe use of the food additive. Special attention should be given to food additive specifications, and/or any other additional information that is needed for the identification and safe use of the food additive under the conditions of its intended use. Current approved animal food additives are found in 21 CFR part 573.

J. Environmental Assessment

FDA is required under the National Environmental Policy Act (NEPA) to consider the environmental impact of its regulatory actions, including those relating to food additives. FDA's regulations in part 25 (21 CFR part 25) set forth procedures to supplement the NEPA regulations of the Council on Environmental Quality (CEQ) under 40 CFR parts 1500-1508. In accordance with 21 CFR 25.20(i), approval of an FAP and approval of a request for an exemption for investigational use of a food additive are both actions that ordinarily require preparation of at least an Environmental Assessment (EA), unless the action is of a class that qualifies for categorical exclusion. An EA is a concise public document that provides sufficient evidence and analysis for CVM to determine whether a Finding Of No Significant Impact (FONSI) can be prepared or an Environmental Impact Statement (EIS) is necessary (21 CFR 25.40). In accordance with 21 CFR 571.1(c) H and 21 CFR 25.15(a), you are required to submit either a claim for categorical exclusion from the requirement to prepare an EA, or an EA under 21 CFR 25.40. In addition, 21 CFR part 25 requires petitions for food additives to include sufficient information to allow the FDA to assess whether environmental impacts may occur from the use and disposal of the food additive.

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A categorical exclusion from the requirement to prepare an EA is defined as a category of actions which do not individually or cumulatively have a significant effect on the human environment (40 CFR 1508.4). The classes of actions for food additives that typically qualify for a categorical exclusion are listed under 21 CFR 25.32. To claim a categorical exclusion from the requirement to prepare an EA you must state in the petition that the intended use qualifies for a categorical exclusion, cite the particular categorical exclusion that is claimed, and state that to your knowledge, no extraordinary circumstances exist (21 CFR 25.15(a) and (d)). FDA will review the petition and determine whether the categorical exclusion is applicable and whether any extraordinary circumstances exist that indicate the intended use of the additive may significantly affect the quality of the human environment.

Some examples of extraordinary circumstances are described in 21 CFR 25.21. These extraordinary circumstances include any actions for which the available data establish that there is potential for serious harm to the environment at the expected exposure level (21 CFR 25.21(a)). Other extraordinary circumstances include actions that may adversely affect a species (flora or fauna) or the critical habitat of a species that is entitled to special protection under a Federal law such as the Endangered Species Act or under the Convention on International Trade in Endangered Species of Wild Flora and Fauna (21 CFR 25.21(b)). Additional extraordinary circumstances are described in the CEQ regulations implementing NEPA (40 CFR 1508.27).

When an EA is necessary, information concerning the purpose and scope of information that you must submit for an EA is contained in 21 CFR 25.40. Data included in the EA can be obtained from the scientific literature and from adequate and controlled laboratory studies.

FDA will evaluate the information contained in the EA to determine whether it is accurate and objective and whether the proposed action may significantly affect the quality of the human environment (21 CFR 25.15(b)). If significant effects requiring the preparation of an EIS are identified, then FDA will prepare an EIS. If such effects are not identified, then FDA will prepare a FONSI.

We recommend that you contact us early in the development of the FAP so that FDA can determine whether the food additive qualifies for a categorical exclusion or to determine the scope of the EA if one is needed. Contact information for the Division of Animal Feeds is provided in section III.A of this document.

IV. OTHER INFORMATION

In accordance with 21 CFR 571.1(a), the FAP must be submitted in triplicate. However, when submitting large data files and statistical analyses, a computer compact disk (CD) can be included instead of sending two of the three paper copies. Furthermore, FDA regulations at 21 CFR 571.1(c) require the information in an FAP be submitted by organizing it according to the lettered headings noted in 21 CFR 571.1(c). If any of the data or information is in a foreign language, accurate and complete English translations must be provided (21 CFR 571.1(a)).

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APPENDIX 1

Food additives used in animal food can be obtained from fermentation or biotechnological processes, including bioengineered microorganisms and plants. For these food additives, the FAP should include a complete description of the manufacturing process including complete descriptions of the following:

- 1) Systematic name (Genus species) and source of each organism or cell line used to produce the food additive.
- 2) Any changes made to the organism and how those changes are accomplished.
- 3) The process used to select or induce cell lines as producers of the food additive.
- 4) Any recombinant techniques used on the organism or cell line, including a complete description of the bioengineering process (e.g., construction of the expression cassettes and the vectors, insertion technique, etc.).
- 5) Any traditional mutagenic techniques used on the organism or cell line.
- 6) The processes and procedures used to maintain organism integrity in response to genetic drift and selection pressure.
- 7) How the master cell and working cell banks are stored, maintained, and inoculums are transferred.
- 8) The media (e.g., fermentation broth) used to cultivate or grow the organism or cell culture. Each ingredient in the media should be identified by appropriate analytical tests and specifications. For other organisms, include a complete description of how the organism is produced and maintained.
- 9) The production or fermentation process, including temperature, time, and pH of the process and all controls that are used to maintain the integrity of the reactor and the media, pre-, post- and during fermentation or production. All analytical control points and methods or process analytical controls used to monitor the manufacturing process should be identified.
- 10) The extraction and purification processes, including the identity and composition of all solvents, precipitants, emulsifiers, and other agents added during these processes.
- 11) The processes and products used to sterilize the reactors.
- 12) The steps taken upon discovery of contamination.

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ENDNOTES

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- ⁱ GFI #187, “Regulation of Genetically Engineered Animals Containing Heritable Recombinant DNA Constructs”
<http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM113903.pdf>
- ⁱⁱ GFI #215, “Target Animal Safety and Effectiveness Protocol Development and Submission”
<http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM241787.pdf>
- ⁱⁱⁱ GFI #53, “Evaluation of the Utility of Food Additives in Diet Fed to Aquatic Animals”
<http://www.fda.gov/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/ucm053413.htm>
- ^{iv} GFI #63, “Validation of Analytical Procedures: Definition and Terminology”
<http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM052377.pdf>
- ^v GFI #64, “Validation of Analytical Procedures: Methodology”
<http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM052379.pdf>
- ^{vi} GFI #3, “General Principles for Evaluating the Safety of Compounds Used in Food-Producing Animals”
<http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM052180.pdf>
- ^{vii} GFI #149, “Studies to Evaluate the Safety of Residues of Veterinary Drugs in Human Food: General Approach to Testing VICH GL33”
<http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM052521.pdf>
- ^{viii} GFI #116, “Studies to Evaluate the Safety of Residues of Veterinary Drugs in Human Food: Genotoxicity Testing VICH GL23”
<http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM052656.pdf>
- ^{ix} GFI #141, “Studies to Evaluate the Safety of Residues of Veterinary Drugs in Human Food: Carcinogenicity Testing VICH GL28”
<http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM052527.pdf>
- ^x GFI #115, “Safety Studies for Veterinary Drug Residues in Human Food: Reproduction Toxicity Testing VICH GL22”
<http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM052655.pdf>

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- ^{xi} GFI #147, “Studies to Evaluate the Safety of Residues of Veterinary Drugs in Human Food: Repeat-Dose (90-Day) Toxicity Testing VICH GL31”
<http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM052523.pdf>
- ^{xii} GFI #148, “Studies to Evaluate the Safety of Residues of Veterinary Drugs in Human Food: Developmental Toxicity Testing VICH GL32”
<http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM052522.pdf>
- ^{xiii} GFI #160, “Studies to Evaluate the Safety of Residues of Veterinary Drugs in Human Food: Repeat-Dose (Chronic) Toxicity Testing VICH GL37”
<http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM052505.pdf>
- ^{xiv} GFI #3, “General Principles for Evaluating the Safety of Compounds Used in Food-Producing Animals”
<http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM052180.pdf>
- ^{xv} GFI #205, “Studies to Evaluate the Metabolism and Residue Kinetics of Veterinary Drugs in Food-producing Animals: Metabolism Study to Determine the Quantity and Identify the Nature of Residues (MRK) VICH GL46”
<http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM207939.pdf>
- ^{xvi} GFI #206, “Studies to Evaluate the Metabolism and Residue Kinetics of Veterinary Drugs in Food-Producing Animals: Comparative Metabolism Studies in Laboratory Animals VICH GL47”
<http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM207940.pdf>
- ^{xvii} GFI #207, “Studies to Evaluate the Metabolism and Residue Kinetics of Veterinary Drugs in Food-Producing Animals: Marker Residue Depletion Studies to Establish Product Withdrawal Periods VICH GL48”
<http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM207941.pdf>
- ^{xviii} GFI #208, “Studies to Evaluate the Metabolism and Residue Kinetics of Veterinary Drugs in Food-Producing Animals: Validation of Analytical Methods used in Residue Depletion Studies VICH GL49”
<http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM207942.pdf>
- ^{xix} GFI #152, “Evaluating the Safety of Antimicrobial New Animal Drugs with Regard to Their Microbiological Effects on Bacteria of Human Health Concern”
<http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM052519.pdf>

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^{xx} GFI #159, “Studies to Evaluate the Safety of Residues of Veterinary Drugs in Human Food: General Approach to Establish a Microbiological ADI VICH GL36(R)”
<http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM124674.pdf>

^{xxi} GFI #185, “Target Animal Safety for Veterinary Pharmaceutical Products VICH GL43”
<http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM052464.pdf>

^{xxii} GFI #215, “Target Animal Safety and Effectiveness Protocol Development and Submission”
<http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM241787.pdf>