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# Pre-Submission Consultation Process for Animal Food Additive Petitions or Generally Recognized as Safe (GRAS) Notices

## Guidance for Industry

### Draft Guidance

*This guidance document is being distributed for comment purposes only.*

Submit comments on this draft guidance by the date provided in the *Federal Register* notice announcing the availability of the draft guidance. Submit electronic comments to <https://www.regulations.gov/>. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with docket number [FDA-2020-D-0064].

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Additional copies of this draft guidance document may be requested from the Policy and Regulations Staff (HFV-6), Center for Veterinary Medicine, Food and Drug Administration, 7500 Standish Place,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

**U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Veterinary Medicine  
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## **Petitions or Generally Recognized as Safe (GRAS) Notices**

### **Draft Guidance for Industry**

*This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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 the Food and Drug Administration's (FDA's) Center for Veterinary Medicine (CVM) recommends be included in:

- (1) pre-petition consultations prior to submission of food additive petitions (FAP) for food additives intended for use in animal food;
- (2) pre-submission consultations regarding an animal food substance<sup>1</sup> for which an entity plans to provide notice of its conclusion that the intended use of the substance is generally recognized as safe (GRAS) under FDA's animal food GRAS Notification program; or
- (3) a Food Use Authorization (FUA) request to permit the use, in human or animal foods, of animal products derived from animals that have been administered an investigational substance<sup>2</sup> intended for use in animal food.

This guidance is intended to help the petitioner, notifier, requestor, firm, stakeholder, or entity (collectively, you) submit information for effective and efficient pre-submission consultations and preparation of an FUA request. This guidance also provides detailed information that will help you navigate FDA's current process for pre-submission consultations and FUA requests.

This guidance also is intended to be used in conjunction with other FDA Guidance for Industry (GFI) documents that are cited in this document. In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

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<sup>1</sup> For this guidance, the term "substance" refers to a proposed use of a substance that may require the submission of an FAP or be the subject of a GRAS conclusion.

<sup>2</sup> For this guidance, the term "investigational substance" refers to a substance that is the subject of a scientific study to support a food additive petition or a GRAS conclusion.

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## II. Background

FDA regulates food under the Federal Food, Drug, and Cosmetic Act (FD&C Act). Section 201(s) of the FD&C Act (21 U.S.C. 321(s)) defines a “food additive,” in part, as “any substance the intended use of which results or may reasonably be expected to result, directly or indirectly, in its becoming a component or otherwise affecting the characteristics of any food.” Section 201(s) excludes from this definition any substance that is generally 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 (for example, new animal drugs or color additives).<sup>3</sup>

On August 14, 2018, the President signed the Animal Drug and Animal Generic Drug User Fee Amendments of 2018 into law (Pub. L. 115-234). This law includes a requirement that FDA publish a guidance relating to the voluntary pre-petition consultation process for food additives intended for use in animal food, including best practices for pre-petition submissions of study protocols and existing data. (See section 306(c) of Pub. L. 115-234). Issuance of this guidance is intended to fulfill that requirement.

Food additives require pre-market approval based on data demonstrating safety and addressing the effect the additive is intended to produce. 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 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. (See section 301(a) of the FD&C Act (21 U.S.C. 331(a)). Therefore, for a firm to lawfully use a food additive in animal food, FDA must have issued a food additive regulation prescribing the conditions under which the additive may be safely used, and the additive must be used in accordance with the regulation. (See section 409(a)(2) of the FD&C Act (21 U.S.C. 348(a)(2)). Section 409(b) through (g) of the FD&C Act and FDA’s regulations located at part 571 in Title 21 of the Code of Federal Regulations (21 CFR part 571) provide for a petition process to establish that a use of an animal food additive is safe. You may find additional information on CVM’s website, “[Ingredients and Additives](#).”<sup>4</sup>

FDA recommends that prior to submitting an FAP, you verify that the substance is not already approved as an animal food additive for your proposed intended use. FDA publishes animal food additive regulations at 21 CFR parts 573 and 579.<sup>5</sup> Furthermore, a particular use of a

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<sup>3</sup> Under section 201(s) of the FD&C Act, the following types of substances are excluded from being animal food additives: (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” (that is, approval granted with respect to use of a substance in food prior to the amendment of the FD&C Act by the Food Additives Amendment of 1958 on September 6, 1958, by the FDA or the United States Department of Agriculture (USDA) pursuant to the FD&C Act, the Poultry Products Inspection Act, or the Meat Inspection Act (21 CFR 570.3(l)); and (5) new animal drugs.

<sup>4</sup> <https://www.fda.gov/animal-veterinary/animal-food-feeds/ingredients-additives>.

<sup>5</sup> Food intentionally subjected to radiation is adulterated, unless the use of the radiation was in conformity with a current food additive regulation or an exemption (see FD&C Act section 402(a)(7)).

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substance may not require an FAP because that use is GRAS. FDA has affirmed certain substances as GRAS for their intended use in animal food and these are listed in 21 CFR parts 582 and 584.

The “[Current Animal Food GRAS Notices Inventory](#)”<sup>6</sup> (Inventory) on FDA’s website lists filed notices in which a firm has notified FDA of its conclusion that the notified substance is generally recognized, among qualified experts, to be safe under the conditions of its intended use and also provides FDA’s response to each notice. The listings in the inventory apply to the specific firm that made the safety conclusion of the use of a substance. However, there is no provision in the FD&C Act or FDA regulations providing exclusivity for a substance that is used in food based on a conclusion that the substance is GRAS under the conditions of its intended use. If you rely on a GRAS notice submitted by another person, you should carefully consider whether its production process, and/or the intended conditions of use of the notified substance, fall within the parameters and specifications addressed by the submitted GRAS notice.<sup>7</sup> For more information about general recognition of safety and the GRAS notification program for animal food, please see 21 CFR part 570, subpart E, GRAS guidance documents, and FDA’s website, “[Generally Recognized as Safe \(GRAS\) Notification Program](#).”<sup>8</sup>

When comparing your proposed use of a substance to existing animal food additive regulations, GRAS affirmation regulations, or GRAS conclusions in the inventory, bear in mind that a food additive regulation, GRAS affirmation, or GRAS conclusion is not for the substance itself, but for the intended use of the substance. Therefore, you may be required to establish a food additive regulation or make a GRAS conclusion if your proposed intended use for a substance is different.

If you intend to submit an FAP or want to participate in the GRAS notification program, FDA encourages pre-petition or pre-notification consultations with FDA, which could include meetings in person, teleconference calls, or video conferences to facilitate the development of information needed for an FAP or a GRAS notice, particularly for those who do not have previous experience preparing an FAP or GRAS notice for animal food. FDA also recommends that you contact FDA early in the development process. A meeting in person, teleconference call, or video conference with FDA staff to discuss a research plan for the use of a substance is often helpful for you to prepare an FAP or a GRAS notice. Once a research plan is developed, FDA strongly suggests that you submit study protocols for FDA's review and receive comments before initiating the studies.

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<sup>6</sup> <https://www.fda.gov/animal-veterinary/generally-recognized-safe-gras-notification-program/current-animal-food-gras-notices-inventory>.

<sup>7</sup> Substances Generally Recognized as Safe, 81 FR 54960 at 54984 and 55013 (Aug. 17, 2016). Available at <https://www.govinfo.gov/content/pkg/FR-2016-08-17/pdf/2016-19164.pdf>.

<sup>8</sup> All available at <https://www.fda.gov/animal-veterinary/animal-food-feeds/generally-recognized-safe-gras-notification-program>.

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### **III. Pre-Submission Consultation Offered by FDA**

FDA offers pre-submission consultation to help facilitate the development of FAPs or GRAS notices for substances intended for use in animal food. Pre-submission consultations are encouraged, but not required. A pre-submission consultation may be used to:

- discuss your proposed intended use of a substance and your plan to address the use of the substance through an FAP or a GRAS conclusion based on the nature of the substance, its intended use, and the type of data available;
- verify whether the quality and quantity of existing information is likely to meet the requirements for an FAP or a GRAS notice;
- address questions about how to establish safe conditions of use of a substance;
- consult with FDA in situations where there are uncertainties about how data may be interpreted and when those uncertainties are of such magnitude that they may affect the outcome of the overall safety determination regarding the use of a substance in animal food (for example, if different but reasonable interpretations of data in a bioassay could change the conclusion regarding the likely carcinogenicity of the substance);
- seek FDA input and recommendations on proposed studies and research methodologies intended to address the safe use of a substance in animal food;
- determine the types of additional data and information that may be needed to meet the requirements of relevant regulatory processes;
- determine whether a proposed intended use of a substance is currently approved or otherwise accepted by FDA; or
- address general questions about approved food additives, investigational substances, FUAs, preparing an FAP, preparing a GRAS notice, or how to legally market a substance for use in animal food in the United States.

The following sections provide: (1) best practices for communication between FDA and entities engaging in pre-submission consultation, including the development of pre-petition or pre-notification submissions of a study protocol and evaluation of the adequacy of existing data from a completed study, and (2) FDA recommendations to facilitate an entity's development of data and information for an FAP or GRAS conclusion. Such recommendations are intended to help ensure that the resulting data and information are useful for evaluating the proposed use of the substance in animal food. A discussion of pre-submission consultation is provided in more detail below.

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**A. Pre-Submission Consultation Meetings and General Correspondence Requests**

As stated above, FDA is available to participate in pre-submission consultation meetings including in-person meetings, teleconference calls, or video conferences. After receiving the request, FDA will schedule a consultation meeting with you.<sup>9</sup>

Alternatively, if you do not intend to participate in a consultation meeting, you may submit written questions as general correspondence to the FDA-CVM Director of the Division of Animal Feeds. FDA will provide feedback in a response letter.

To request a consultation meeting or to send general correspondence inquiries, you may contact the Division of Animal Feeds in FDA/CVM in the following ways:

Mail: Director, Division of Animal Feeds  
Center for Veterinary Medicine  
US Food and Drug Administration  
MPN 4, HFV 220  
12225 Wilkins Avenue  
Rockville, MD 20852

Email: [Animalfood-premarket@fda.hhs.gov](mailto:Animalfood-premarket@fda.hhs.gov)

**B. Investigational Food Additive (IFA) File for Animal Food**

In addition to pre-submission consultation meetings and general correspondence requests, FDA's CVM has a process known as the Investigational Food Additive (IFA) file. Using an IFA file, you can exchange confidential data, ideas, and information with FDA while you investigate the safety and utility of a substance for its intended use and consider whether to submit an FAP or a GRAS notice. The IFA file process is discussed below.

FDA will open an IFA file, at your request, to provide you the opportunity to receive feedback from FDA while you investigate the safety of the intended use of a substance in animal food. You may share data or information with FDA to obtain FDA scientific and regulatory expertise and insight. The types of IFA submissions that FDA reviews include: (1) study protocols, (2) FUA requests, and (3) evaluations of the adequacy of existing data from completed studies.

An IFA file submission can address one, all, or a combination of issues, such as chemical composition, target animal safety, human food safety, and the impact on the environment of the proposed use of a substance in animal food. A submission to an IFA file is not required to contain all the elements specified in the regulations for an FAP or a GRAS notice.

FDA does not acknowledge the existence of, or announce the establishment of, an IFA file.<sup>10</sup> There are no legally specified time frames for the review of a submission to an IFA file, but FDA

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<sup>9</sup> There are additional clearance procedures for non-U.S. citizens requesting an in-person meeting at FDA offices. For details, refer to Program Policy and Procedures Manual 1240.2601, <https://www.fda.gov/media/70190/download> or you may email FDA at [Animalfood-premarket@fda.hhs.gov](mailto:Animalfood-premarket@fda.hhs.gov).

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has created internal goals that are listed throughout this guidance. FDA’s response to an IFA file submission is shared only with the entity that established the IFA and with third parties formally authorized by the entity.

You cannot “test market”<sup>11</sup> a substance until a food additive regulation is established for its use or, until you have reached a GRAS conclusion for the intended use; this prohibition includes the time during which FDA is reviewing your IFA file submission(s).

While the information submitted to an IFA file will include some or all of the same information typically provided later in an FAP or a GRAS notice, the FAP or GRAS notice is independent of the IFA file. You will need to submit all data and information required for an FAP or a GRAS notice, even if you have an existing IFA file that contains such information.

If the information to be submitted to an IFA file does not fit into one of the following submission types, it can be identified and sent to FDA as general correspondence.

You may submit information such as the following to an IFA file:

*1. Request for Review of a Study Protocol*

FDA recommends that entities submit a protocol for a study, not yet initiated, that is intended to generate pivotal data to support the utility, safety, stability, or homogeneity of a substance intended for use in animal food. For the purposes of this guidance, pivotal data means data that provide the primary basis for a decision or conclusion regarding the proposed use of a substance in animal food or the hypothesis to be tested in a study (for example, a hypothesis that a substance can be homogeneously mixed into swine feed). A study protocol may be submitted for review during the research and development of a substance. Additionally, you may include any preliminary data generated prior to drafting the study protocol you intend to initiate to provide context for the submitted protocol (for example, data from a pilot study or method validation). FDA’s protocol review can also include an assessment of an analytical method used to generate data in support of a proposed use of a substance, and associated method validations.<sup>12</sup> FDA has set the following goals (from the date of submission receipt) to provide a response letter following review of a study protocol review request:

- Study protocol without method validation or preliminary data: 50 days from the date of submission receipt
- Study protocol with method validation or preliminary data: 130 days from the date of submission receipt

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<sup>10</sup> Please see section VI for a discussion of IFA file treatment under the Freedom of Information Act.

<sup>11</sup> Test marketing is a tool used to generate insight into the potential market success of a new product, prior to its formal launch to a wider customer base. For an animal nutrition business, this may involve allowing a new product to be used in animal food by a select group of customers.

<sup>12</sup> Method validation is the process that helps confirm that the analytical method used is suitable for its intended purpose of analyzing a single analyte or a set of analytes.

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- Analytical method development and validation: 130 days from the date of submission receipt

For review of a study protocol for a study to address the utility, safety, stability, or homogeneity of a substance, FDA will primarily be guided by the definition of safety in 21 CFR 570.3(i) and information in the current publications of the National Academies of Sciences, Engineering, and Medicine-National Research Council (see 21 CFR 570.20). Additionally, FDA will consider in our evaluation, principles of experimentation to help ensure that you design and conduct adequate and well-controlled studies. The types of information discussed in Appendix 2 form a general framework that FDA uses when evaluating a study protocol based on the above criteria. FDA will not review a protocol for a study that has already been initiated.

When your study is complete, you may submit a final study report (FSR) to FDA as part of a pre-submission consultation. You may also use the FSR format to submit data from a completed study in an FAP, or as applicable, a GRAS notice. Please see below for a detailed discussion of the FSR in section [III.B.3. Request for Review of the Adequacy of Existing Data from a Completed Study](#).

### *2. Request for Authorization for Use of Animal Products in Human or Animal Foods (FUA Request)*

If products, such as meat, milk, or eggs from animals used in studies to support the safety or utility of a substance are intended to be used for human or animal food, you must obtain a food use authorization (FUA) from FDA or USDA to permit the use of these products (see 21 CFR 570.17(b)).

FDA will review an FUA request to ensure that the submitted information adequately addresses whether food products, such as meat, milk, or eggs, that came from the investigational animals that were administered the substance are safe for humans and animals to consume. If the submitted information shows that the consumption of the food products is consistent with the public health and the food does not contain unsafe levels of residues or metabolites of the investigational substance, FDA generally provides an FUA for a specific number of investigational animals. FDA has set the following goal (from the date of submission receipt) to provide a response letter following review of an FUA request:

- FUA request: 130 days from the date of submission receipt

### *3. Request for Review of the Adequacy of Existing Data from a Completed Study<sup>13</sup>*

You can submit data from completed experiments to receive preliminary feedback from FDA on the adequacy and suitability of the data to support relevant sections of an FAP. FDA may: (1) comment on the appropriateness of data or deficiencies present, (2) suggest ways to rectify deficiencies, if possible (such as changes to the statistical analysis), and (3) recommend further evaluations or additional studies.

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<sup>13</sup> For purposes of this guidance, “study” means an experiment, test, or trial.

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FDA's assessment of data will be based principally on whether: (1) the data generated are from experiments that were conducted based on accepted scientific methods and principles of experimentation, (2) procedures were followed that reflect animal feeding and husbandry practices used in the United States, and (3) nutritional requirements and maximum tolerable levels proposed by the National Academies of Sciences, Engineering, and Medicine-National Research Council were reasonably met.

When FDA evaluates your submission, data generated from studies conducted in foreign countries, meaning countries other than the United States, undergo the same assessment process as data generated in the United States. For the purposes of this guidance, FDA considers foreign data to be data generated outside the United States both by entities based within or outside the United States.

Based on its preliminary assessment, FDA will provide a written response about the adequacy of data you submitted to support the safety of the potential use of a substance in animal food. In the event additional data are required to adequately support such use, FDA will provide relevant recommendations, including our scientific rationale for requesting any additional data or information. Unpublished existing data from completed studies can be used to support determinations in an FAP. However, if you intend to use unpublished data to make a GRAS conclusion about the use of a substance, you must explain how there could be a basis for a conclusion of GRAS status if qualified experts do not have access to such data and information (see 21 CFR 570.250(e)).

FDA has set the following goal (from the date of submission receipt) to provide a response letter based on the review of existing data from a completed study:

- Request for review of the adequacy of existing data from a completed study: 180 days from the date of submission receipt

**C. What to Include in a Request to Establish an IFA File**

In addition to providing your name, address, and other contact information, the Agency recommends that you provide the following identifying information about the substance and its intended use when requesting to establish an IFA file:

- common or usual name of the substance you intend to investigate;
- proposed intended use of the substance;
- target animal species for which you intend to investigate the proposed use of the substance; and
- an Environmental Assessment (EA) or a request for a Categorical Exclusion (CE) from preparation of an environmental assessment, including a statement that no extraordinary circumstances exist (see section [V. Environmental Assessment](#) for more details).

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If you will be submitting and discussing information with FDA on another entity's behalf, you must provide an original letter of authorization signed by the entity. FDA recommends an accurate and complete English translation for any data or information presented in a foreign language.<sup>14</sup>

Once you have received your IFA file number, please refer to it in any future correspondence for matters under the scope of that IFA file. In addition, FDA recommends that for each submission type, you provide information to your IFA file as described below.

### **D. What to Include in Each Submission Type to an Established IFA File**

#### *1. Request for Review of a Study Protocol*

The recommended content and format for a study protocol is provided in [Appendix 2 – Study Protocol Content for a Substance Intended for Investigational Use in Animal Food](#). The study protocol content guideline serves as an outline of information that FDA recommends be included to provide the purpose of a study and to explain how a proposed study will be conducted. The items included in the guideline are based on the information you would include in a study report or published scientific article that may be used to support an FAP or GRAS conclusion.

While preparing a study protocol, FDA recommends that you follow Appendix 2 as closely as possible to provide clear descriptions of the design, materials, methods, steps, and other processes involved in the proposed study. However, not all items may apply to your proposed study or you may have additional information to include.

The goals of the Study Protocol Content Guideline in Appendix 2 are to:

- suggest a uniform format for writing a study protocol;
- provide a reference of essential items that should be considered for inclusion in a study protocol;
- facilitate the development of a detailed and complete study protocol;
- help make the protocol more user-friendly;
- enable FDA reviewers to evaluate the study protocol efficiently and convey their comments in terms clearly understood by entities across different geographical locations in the world; and
- reduce the number of significant amendments to a study protocol.

You may use the study protocol format or you may choose to follow alternative procedures to design and conduct a study intended to generate data to support regulatory submissions.

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<sup>14</sup> While information you provide for the pre-petition consultation process is voluntary, FDA's regulations require an accurate and complete English translation of any material submitted in a foreign language as part of an FAP (see 21 CFR 571.1(a)).

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### ***2. Request for Authorization for Use of Animal Products in Human or Animal Foods (FUA Request)***

You should include in your FUA request data to show that consumption of food derived from animals given the maximum levels of the investigational substance with the minimum withdrawal periods (if any) will be consistent with the public health and the food will not contain unsafe levels of residues or metabolites of the substance. You also should include the name and location of the packing plant where the animals will be processed; however, you may request a waiver. FDA may place terms on a waiver grant, such as an additional holding time prior to slaughter.

You should include the following in your request for an FUA (where applicable):

- a description of the investigational substance, and its composition, including any preservatives, diluents, carriers, or other relevant components;
- the form in which the substance will be fed (for example, powder, liquid, pellets, granules);
- the maximum use rate that the investigational substance will be administered to investigational animals (for example, 300 parts per million in the complete diet, 150 grams per animal per day, one kilogram per metric ton of diet);
- information on how the substance will be delivered to the animals for consumption (for example, top-dressed on food, mixed into complete diet, added to drinking water);
- the animal species that will receive the substance, including the class (for example, growing, adult, breeding) and age;
- the number of animals that are expected to receive the substance<sup>15</sup>;
- a brief description of the study design, including composition of the experimental diets;
- frequency of feeding and timing of substance administration;
- maximum duration of substance administration;
- the period for which investigational animals will be held prior to slaughter after administration of the substance has stopped (withdrawal period). A withdrawal period can vary depending on the animal, the substance, and the nature and safety of the investigational use of the substance, and could include a zero-day withdrawal<sup>16</sup>;
- any other restrictions for using the substance or its conditions of use; and

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<sup>15</sup> The total number of animals you request in your FUA should reflect the actual number of animals you intend to treat with the investigational substance in a single study multiplied by the number of times that you plan to repeat the study.

<sup>16</sup> If consistent with public health, a zero-day withdrawal period should be requested for the use of milk from investigational animals.

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- a summary narrative, based on proprietary information and a literature review, as applicable, to address the safety of the proposed investigational use of the substance.

#### *3. Request for Review of the Adequacy of Existing Data from a Completed Study*

You may submit data generated from a completed study to FDA for review, preferably in the form of an FSR. The FSR is a complete and comprehensive description of a study, the resulting data, the analysis, and conclusions. The FSR is written after the study is completed to properly document and present all relevant details about the study. An FSR is often used to support an FAP. FDA recommends you use the FSR format in [Appendix 3 – Investigational Animal Food Substance Final Study Report Format](#): (1) to report data and information generated from a completed study, whether generated within or outside (foreign data) the United States, and (2) to document data and information you generate in any future studies, including studies based on study protocols previously discussed with FDA.

Using a standardized FSR format will result in more efficient FDA review of your submitted data and information that will be a basis of regulatory decisions for an FAP. The FSR should include information from the list provided in Appendix 3 that is applicable to the completed study. The list provided is not exhaustive and is intended to provide a general framework for preparing an FSR.

The FSR may be prepared by the study sponsor, the investigator, or both, through a collaborative effort. All individuals or entities involved in the preparation of an FSR should be considered authors. The FSR should include a document signed and dated by the study director (or the individual responsible for the overall conduct of the study) describing the contribution provided by each author and attest to the accuracy and completeness of the FSR.

Conducting nonclinical laboratory studies to support safety in compliance with the Good Laboratory Practice for Nonclinical Laboratory Studies (GLP) regulations helps ensure the quality and integrity of the resulting data (see 21 CFR part 58). FDA recommends that an FSR include a statement identifying the parts of the study conducted in accordance with these regulations. If the study or a part of the study was not conducted in accordance with GLP regulations, the reasons why should be included in the FSR.<sup>17</sup>

As noted earlier, unpublished existing data from completed studies can be used to support determinations in an FAP. However, if you intend to use unpublished data to make a GRAS conclusion about the use of a substance, you must explain how there could be a basis for a conclusion of GRAS status if qualified experts do not have access to such data and information (see 21 CFR 570.250(e)).

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<sup>17</sup> While information you provide regarding nonclinical laboratory studies for the pre-submission consultation process is voluntary, FDA's regulations require an FAP to include either a statement that the study was conducted in compliance with the requirements set forth in 21 CFR part 58 or a brief statement of the reason for noncompliance if the study is not conducted in compliance. (See 21 CFR 571.1(k)).

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### **E. How to Submit Information to an IFA File**

To establish an IFA file or add documents to an existing IFA file, FDA recommends you submit such information through the CVM eSubmitter Application. The CVM eSubmitter Application is an electronic, question-based submission software to create files that can be transmitted electronically to CVM through its secure Electronic Submission Gateway (ESG). CVM's eSubmitter uses data-capturing templates to allow you to assemble a complete and appropriately structured submission to CVM. For detailed explanations on how to submit information through the eSubmitter tool, you may reference FDA's website, "[Electronic Submissions](#)."<sup>18</sup> You may also reference GFI #108, "[Registering with CVM's Electronic Submission System](#)."<sup>19</sup>

Though electronic submission is preferred, you may also submit information by mail to the following address;

Director, Division of Animal Feeds  
Center for Veterinary Medicine  
US Food and Drug Administration  
MPN 4, Room 2658  
12225 Wilkins Avenue  
Rockville, MD 20852

Additionally, information may be submitted by email to [Animalfood-premarket@fda.hhs.gov](mailto:Animalfood-premarket@fda.hhs.gov).

### **IV. FDA Response to Requests Submitted to an IFA File**

In response to your request for review of pre-submission consultation information submitted to an IFA file, FDA will convey comments from its review in a letter to you. FDA will strive to respond within the number of days indicated earlier in this document; however, FDA response time is also dependent on other FDA regulatory priorities. If review of a study protocol without accompanying data is expected to exceed 50 days, FDA will notify you using the same method of communication you chose for your study protocol submission.

### **V. 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 the investigational use of a substance. FDA's regulations in 21 CFR part 25 set forth procedures to supplement the NEPA regulations published by the Council on Environmental Quality (CEQ) in 40 CFR parts 1500-1508. Under 21 CFR 25.15(a), all applications or petitions requesting Agency action require the submission of an Environmental Assessment (EA) or a claim of categorical exclusion. In accordance with 21 CFR 25.20(i), approval of an FAP and approval of a request

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<sup>18</sup> <https://www.fda.gov/animal-veterinary/development-approval-process/electronic-submissions>.

<sup>19</sup> <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/cvm-gfi-108-registering-cvms-electronic-submission-system>.

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for an exemption for investigational use of a substance are both actions that normally require preparation of at least an EA, unless the action is of a class that qualifies for categorical exclusion.

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 and which have been found to have no such effect in procedures adopted by a Federal agency in implementation of the NEPA regulations (see 40 CFR 1508.4). The classes of actions for substances to be used in animal food that typically qualify for a categorical exclusion are listed under 21 CFR 25.32. The establishment of an IFA and actions under that IFA will ordinarily qualify for a claim of categorical exclusion under 21 CFR 25.32(b), “[a]ction on a request for exemption for investigational use of a food additive if the food additive to be shipped under the request is intended to be used for clinical studies or research.”

To claim a categorical exclusion from the requirement to prepare an EA, you must state in your request to establish an IFA that the intended use qualifies for a categorical exclusion, cite the particular categorical exclusion that is claimed (e.g., 21 CFR 25.32(b)), and state that, to your knowledge, no extraordinary circumstances exist (21 CFR 25.15(a) and (d)). FDA will review the claim of categorical exclusion and determine whether the categorical exclusion is applicable and whether any extraordinary circumstances exist that indicate the intended use of the investigational substance may significantly affect the quality of the human environment. Examples of extraordinary circumstances described in 21 CFR 25.21 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)), and actions that may adversely affect a species (flora or fauna) or the critical habitat of a species that has been determined to be endangered or threatened under the Endangered Species Act or under the Convention on International Trade in Endangered Species of Wild Flora and Fauna, or that is entitled to special protection under some other Federal law (21 CFR 25.21(b)). If you make a claim of categorical exclusion you may consider providing the following language, as outlined in (21 CFR 25.15(a) and (d)):

*We are requesting a categorical exclusion from preparation of an environmental assessment or an environmental impact statement for the investigational use of <insert investigational food additive name> as provided in 21 CFR 25.32(b). To our knowledge, no extraordinary circumstances exist that indicate the specific proposed action may significantly affect the quality of the human environment.*

If extraordinary circumstances are identified, preparation of an EA will be necessary (see 21 CFR 25.21). If you think an EA may be needed, FDA recommends that you contact CVM to schedule a pre-petition consultation meeting to discuss the requirements of an EA for the proposed investigational use of a food additive.

Information concerning the preparation of 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 well-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 25.40(e)). If significant effects requiring the preparation of

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an Environmental Impact Statement (EIS) are identified, then FDA will prepare an EIS. If such effects are not identified, then FDA will prepare a finding of no significant impact (FONSI).

**VI. Freedom of Information Act**

Information submitted to FDA is considered a record and is subject to a Freedom of Information Act (FOIA) request under 21 CFR part 20. However, information submitted as part of a pre-submission consultation to an IFA can be considered information submitted voluntarily to FDA relating to an ingredient or product under development. In accordance with 21 CFR 20.111(d), such data and information ordinarily would not be available for public disclosure until referenced or presented publicly by you. If pre-submission information contained in an IFA file is later submitted to FDA in an FAP or a GRAS notice, that information would be subject to the disclosure provisions under 21 CFR 571.1(h) or 21 CFR 570.275, depending on whether the information is included in an FAP or GRAS notice, respectively.

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**Appendix 1 – Table of Abbreviations and Acronyms Used in this Guidance**

| ABBREVIATION OR ACRONYM | WHAT IT MEANS                             |
|-------------------------|---|
| CE                      | Categorical Exclusion                     |
| CEQ                     | Council on Environmental Quality          |
| CFR                     | Code of Federal Regulations               |
| CVM                     | Center for Veterinary Medicine            |
| EA                      | Environmental Assessment                  |
| EIS                     | Environmental Impact Statement            |
| ESG                     | Electronic Submission Gateway             |
| FAP                     | Food Additive Petition                    |
| FDA                     | U.S. Food and Drug Administration         |
| FD&C Act                | Federal Food, Drug, and Cosmetic Act      |
| FOIA                    | Freedom Of Information Act                |
| FONSI                   | Finding Of No Significant Impact          |
| FR                      | Federal Register                          |
| FSR                     | Final Study Report                        |
| FUA                     | Food Use Authorization                    |
| GLP                     | Good Laboratory Practice                  |
| GFI                     | Guidance For Industry                     |
| GRAS                    | Generally Recognized As Safe              |
| IFA                     | Investigational Food Additive             |
| NEPA                    | National Environmental Policy Act of 1969 |
| NRC                     | National Research Council                 |
| SOP                     | Standard Operating Procedure              |
| USC                     | United States Code                        |
| USDA                    | United States Department of Agriculture   |

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**Appendix 2 – Study Protocol Content for a Study of a Substance Intended for Investigational Use in Animal Food**

The following is the general, recommended content of a study protocol for a study of a substance intended for investigational use in animal food. You should make any adjustments needed to address the purpose of your particular study.

**1. TITLE**

Provide a descriptive title containing the purpose, substance, and subject of the proposed study.

**2. UNIQUE IDENTIFIER FOR THE STUDY**

Located on the title page, the unique identifier should include a study protocol number, the status of the study protocol (for example, draft, final, amended), and the date of the study protocol version.

**3. STUDY LOCATION(S)**

Provide the identities and location of study sites, including those where analytical and statistical work will be conducted (including contract facilities).

**4. STUDY CONTACTS**

Include the investigator(s), sponsor representatives, and all other participants responsible for major aspects of the study, such as study monitors, consultants (for example, veterinarian, pathologist, or statistician), and quality assurance personnel. For each contact, list the title, qualifications, and summary of professional background (or attach a curriculum vitae), as well as the email address, postal address, telephone number, and any other methods of communication.

**5. PROTOCOL OBJECTIVE(S)**

Define objective(s) of the protocol (for example, determine target animal safety, establish utility or functionality).

**6. STUDY OBJECTIVE(S)**

Include the following when applicable:

- A. *Pivotal/Non-Pivotal Studies* - Determine and document whether the study will be pivotal or non-pivotal. Pivotal studies are those used to generate data that provide the primary basis for a decision or conclusion regarding the investigational substance and the premise that is to be tested in the study (for example, the substance can be

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homogeneously mixed into swine feed, or the substance achieves the intended purpose). Non-pivotal studies are those that are used to generate data that provide a secondary or supporting basis for a decision or conclusion regarding the investigational substance.

- B. *Standards applied* - Define any standards that will be applied to the conduct of the studies (for example GLP).
- C. *Justifications* - State, where applicable, information relevant to understanding the study objectives, such as data or information from scientific publications or pilot studies that justify the conduct of the study.

## **7. STUDY SCHEDULE**

Include the proposed date(s) of initiation, schedule of events, and proposed date(s) of completion.

## **8. STUDY DESIGN**

Include information, such as treatment groups, experimental design (for example, cross-over, Latin Square, randomized complete block, split-plots), experimental unit (for example, pen, individual animal), blocking factor(s), randomization procedures, such as allocation of animals to treatment groups and allocation of treatment groups to experimental units, and blinding. Experimental units should be specified, and its selection justified, so that statistical analysis of data is based on the specified experimental unit.

## **9. STUDY PROCEDURES**

- A. *Description of Test Animals* – Provide descriptions of test animal(s) including: (1) age (parity, if applicable), (2) sex, (3) breed and class, (4) initial body weight, (5) physiological state (for example, lactating, growing), (6) number of animals, (7) source of animals, (8) identification method (animal selection and identification, tattoo, neck band, wing band, brand, or other method of identification), and (9) any other relevant details.
- B. *Inclusion/Exclusion/Post Inclusion Removal Criteria* – Provide inclusion, exclusion, and post-inclusion removal criteria. Inclusion criteria is a list of conditions that must be met by each study animal (for example, age, body weight, health status) prior to placement in the study. Exclusion criteria is a list of conditions that would preclude an animal from being included in the study (for example, illness, deformities, stunted growth). Post-inclusion removal criteria include information regarding why an animal would be removed from the study after initial inclusion. For post-inclusion removal of animal(s) from the study, provide: (1) qualitative and quantitative criteria for removal, (2) procedures for removal of animals from the study, and (3) fate of removed study animals.

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- C. *Acclimation of Test Animals* – Provide information regarding the acclimation of experimental animals, including: (1) duration, (2) medication and vaccination during acclimation period, and (3) the baseline data collected prior to initiating the study, if any.
- D. *Study Blinding* – Describe: (1) the extent of blinding (for example, monitor, investigator), (2) the blinding method(s) and procedure(s) used, and (3) the list of personnel who will have access to treatment codes.
- E. *Analytical Methods* – Ensure that details of the analytical methods described in the protocol: (1) identify the analytical measurement(s) to be made and explain their relevance to protocol objectives, (2) specify the analytical plan to be used, including a summary of the method(s), provide a description of procedures for sample selection, collection, preparation, and storage, evidence of analytical method validations, a description of the validation plan when the method is being developed for the study, the quality control procedures for the method, and the criteria and procedures used to assess analytical results, (3) reference and summarize relevant scientific literature supporting the use of the analytical method for the intended measurements, and (4) if applicable, provide documentation that relevant validations have been completed before the initiation of the study. All validation data and information should be provided as a separate section.
- F. *Study Facilities* – Provide information regarding study facilities, including containment equipment (cages, pens, runs, stalls, etc.) and space allocation per animal (compare to typical United States management practices), lighting equipment (if controlled, define photo period), heating and cooling equipment (define temperature goals), ventilation equipment, feeding equipment, watering equipment, and a facility diagram. The facility diagram should include: (1) orientation of building, (2) location of feeding and watering equipment, (3) placement of ventilation system, (4) location of lighting, (5) pen or cage dimensions, (6) orientation of experimental blocks, (7) treatment codes, and (8) position of environmental and weather recording devices.
- G. *Investigational Substance and Control Articles* – Provide information regarding the investigational substance and control articles. Identify the investigational substance and provide details of its characterization and specifications. In addition, state the control article(s) to be used in the study, if any, and provide its specifications. Details, such as chemical name, trade name, lot number, and manufacture and expiration dates, of the substance and control articles should be provided. Instructions for further mixing (if any), packaging, and storage of these articles should be stated. If administered in drinking water, a complete description of how the substance will be incorporated in the water should be provided. Additionally, relevant Safety Data Sheets (SDS) should be provided for the substance and control articles. The specifications of the substance evaluated in investigational studies

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should be similar or identical to the specifications of the substance that will be the subject of your FAP or GRAS notice.

- H. *Experimental Diet Formulation(s)* – Include the following elements in your description of the experimental diet formulations: (1) ingredient list(s), (2) nutrient and investigational substance concentrations in experimental diet(s), (3) food or water sampling procedure(s), (4) food form, and (5) the manufacture of experimental diets. These elements are explained below.

Ingredient lists: describe all ingredients using their common or usual name. All ingredients used in experimental diets should reflect acceptable animal diet formulations and feeding practices in the United States.

Nutrient and investigational substance concentration(s) in experimental diet(s): include the calculated nutrient concentration (for example, amount of protein, fiber, vitamins, minerals), along with the assay procedure(s) (and the analytical laboratory, including address and telephone number) that will be used to confirm the accuracy of the calculated dietary values. In addition, provide the quantitative composition of all food components or ingredients in the diet (for example, amount of corn, soybean meal, wheat).

The food form description: specify the form to be used, such as mashed, crumbled, or pelleted.

Manufacture of experimental diets: provide details regarding the procedures, facilities, and equipment to be used by the manufacturer of the experimental diets.

Recommendations in reference sources, such as the National Academies of Sciences, Engineering, and Medicine-National Research Council publications, may serve as useful guides in determining the nutritional requirements of the study animals and the preparation of food. Diet-related study documentation should demonstrate that the objective of the study can be accomplished while meeting the animals' nutritional and associated welfare requirements. Detailed records of food characteristics should be collected in instances where nutritional status can be critical to the measurements to be collected in the study.

- I. *Experimental Treatment Administration* – Provide the feeding program or schedule for feeding the experimental diets, including the amount of the substance and how it will be administered (for example, mixed in food, top-dressed, mixed in water). Provide the frequency and duration of feeding and state whether animals will be allowed ad-libitum feeding, limit feeding, or pair-feeding (food amounts matched between controls and substance-treated animals).
- J. *Concurrent/Concomitant Medications/Therapies/Vaccinations/Fate of Treated Animals* – List the medications, vaccinations, or other therapies concurrently administered to experimental animals. Describe the fate of animals that are subjected

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to medications during the course of the study and that of animals euthanized due to welfare concerns.

- K. *General management practices* – Include information regarding general management practices such as the frequency of personnel visits to the study facility, frequency of checking feeders and waterers, frequency of adding food to feeders, and frequency of checking for temperature and humidity. Provide details regarding the watering program, the lighting program, and animal welfare checks. Include the facility cleaning schedule, daily monitoring, and any other feeding or management program details important to the study.
- L. *Provisions for necropsy and disposal of expired test subjects* – Describe when, where, and who will conduct necropsy examination of animals that die during the study and how these animals will be disposed of.

## **10. SPECIFICATION OF PARAMETERS TO BE ASSESSED**

- A. *Pivotal parameter(s)* – Specify: (1) which parameters will be assessed, (2) when treatment responses for each parameter will be assessed, (3) equipment and procedures for assessing these responses, (4) forms for capturing source data, (5) calculation(s) for derived data, and (6) name(s) and address(es) of outside laboratories used for substance or sample analysis.
- B. *Supporting parameters* – Record: (1) which parameters are supporting parameters, (2) when treatment responses for these parameters will be assessed, (3) equipment and procedures for assessing these responses, and (4) calculation of derived data.

Units used to measure parameters should be clearly stated and transformation of units or conversion factors should be indicated and documented. When possible, laboratory analysis data should be recorded on a record sheet and reference values for the parameters used by the laboratory should be presented along with the data. Source for the reference values should be provided, if available.

## **11. STATISTICAL ANALYSIS OF DATA**

Provide a plan for statistical analysis of the data appropriate to the chosen study design and the parameters to be evaluated. Details of the analysis procedure should be provided. When including this information, identify: (1) the experimental unit, (2) the number of replicates per treatment and provide details of a power analysis, if applicable, (3) the statistical methodology with detailed descriptions of data analysis and treatment means separation, hypothesis to be tested or parameters to be estimated, assumptions that are being made, and model specification, if a model is to be used, and (4) how the statistical results will be used to draw conclusions about the study's objectives.

## **12. COLLECTION AND RETENTION OF SOURCE DATA**

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Include information about the following issues:

- A. *Data collection* – Describe how raw data, either handwritten or electronic, will be recorded in a permanent medium (for example, ink for written records or electronic records that are unalterable) that can be traced by signature and date to the respective individual(s) who recorded the data.

Ensure that data will be collected for all relevant parameters indicated in the study protocol. Source data should be original, accurate, legible, organized, and recorded at the time the observation is made. Authenticate and provide an explanation in the record for any data that need to be transcribed or copied for legibility.

Corrections in handwritten study documentation should be made by drawing a straight line through the original entry, with the original entry still legible. Date, initial, and provide the reason for the correction. If data are captured electronically, a generally accepted system should be set up to authenticate any changes made to such data.

- B. *Data Retention* – Store all data, information, and other study documentation in a manner that protects them from deterioration, destruction, or tampering, in accordance with the nature of the records. The storage site should allow the orderly storage and easy retrieval of retained data.

Retain all study documents until after FDA has issued a food additive regulation based on the petition or has denied the food additive petition in accordance with 21 CFR 571.100(a), or until the petitioner has withdrawn the petition, in accordance with 21 CFR 571.7. Although the GRAS final rule does not specify any timeframe to retain the data and information that support a conclusion of GRAS status, preservation of the data and information that are the basis for the conclusion of GRAS status represents prudent practice for those who claim an exclusion from a statutory requirement regardless of whether FDA is subsequently notified (81 FR 54959 at 54992).<sup>20</sup>

**13. AMENDMENT TO THE PROTOCOL/DEVIATION FROM THE PROTOCOL**

Include how protocol amendments or deviations will be addressed during the conduct of the study.

- A. *Amendments* – The investigator and the study site(s) personnel (if applicable) should document, sign, and date any amendments made to the protocol. Protocol amendments should include a justification. A copy of the signed protocol and any amendments should be maintained at the study site.

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<sup>20</sup> <https://www.federalregister.gov/documents/2016/08/17/2016-19164/substances-generally-recognized-as-safe>.

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- B. *Deviations* – The investigator and study site(s) personnel should record and promptly report deviations to the study sponsor and these should be authorized by the sponsor in writing.

**14. INVESTIGATIONAL SUBSTANCE DISPOSITION/ANIMAL ACCOUNTABILITY/FOOD DISPOSITION/FOOD ACCOUNTABILITY**

Document the accountability of all investigational substances used and the disposition of all unused investigational substances, unused food, and animals used. You must obtain food use authorizations, if products from animals that consume the substance are intended for use as human or animal food. (21 CFR 570.17(b)). Food use authorization should be obtained prior to conducting the study. See section [III.D.2. Request for Authorization for Use of Animal Products in Human or Animal Foods \(FUA Request\)](#) above.

**15. PROTOCOL APPROVAL SIGNATURES**

Obtain dated signatures from the study leadership (for example, project manager, study sponsor, investigator, study monitor, quality assurance representative, consultant) on the protocol, including any amendments to the protocol, to indicate approval of the protocol and agreement to follow it.

**16. APPENDICES**

Include relevant appendices, such as a description of sample collection(s), description of sample preparation, description of special equipment, analytical methods, and validation techniques employed, and standard operating procedures (SOPs).

### **Appendix 3 – Investigational Animal Food Substance Final Study Report Format**

The following is the general, recommended content of a final study report (FSR) for an investigational substance intended for use in animal food. You should make any necessary adjustments needed to address the purpose of your particular report.

#### **1. Title of the study**

Provide a descriptive title containing the purpose, investigational substance, and subjects of the study.

#### **2. Unique Identifier for the study report**

Located on the title page, the unique identifier should include a study report number, the status of the study report (such as, final or amended), and the date of the version of the study report.

#### **3. Study Objectives**

State the purpose, type of study, name of the substance evaluated, target animal, and any other information relevant to the study objectives.

#### **4. Study personnel**

Provide the title or roles played, qualifications, summary of professional background (or attach a curriculum vitae), and contact information including postal address, telephone number, and email address for all study personnel. Study personnel may include the investigator(s), representatives of the sponsor, study monitor(s), quality assurance and quality control personnel, consulting veterinarian(s), pathologist(s), statistician(s), and all other participants in the study.

#### **5. Study location(s)**

Provide the identities and location of study sites, including those where analytical and statistical work were conducted (including contract facilities).

#### **6. Key study dates**

Include key study dates such as the start and finish dates for the study, dates of sample collection and analyses, dates of study termination, database lock date, and dates of statistical processing of data.

#### **7. Study design**

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Include the type and description of study design (for example, cross-over, Latin Square, randomized complete block, split-plots). Treatments, replicates, blocking factors, randomization procedures, and any other design components should be addressed. The experimental unit should be specified, and its selection justified, so that statistical analysis of data is based on that specified experimental unit.

#### **8. Materials and methods**

Include details of materials and methods of the study, such as animal selection and identification, characterizations and compositions of the substance and control article(s), treatment diets used, analyzed dietary nutrient compositions, treatment blinding to study personnel, study animal selection (including details of inclusion, exclusion, and removal criteria), duration of acclimation, treatment and observation periods, removal of study animals during the course of the study, necropsy details, disposal of investigational substance, and any other substances, resources, approaches or procedures of the study. Materials and methods also include details of data collection, in addition to sample collection, processing, handling, and storage. Description of the analytical methods used in the study, including any applicable assay methods used to determine the investigational substance or relevant metabolites in food, water, body fluids, or tissues, should be included.

#### **9. Housing and animal management**

Include details of how the animals were housed and maintained during the study. This includes details of animal housing (for example, cage or litter for broiler chickens, pens or pasture for cattle), feeding, watering, ventilation, heating and cooling, lighting schedules, welfare checks, food addition, food withdrawal, animal weighing, sample collection, euthanasia of animals, and any other details about how the animals were housed, maintained, and handled during the study.

#### **10. Statistical methods**

Describe the statistical methods used to analyze the data generated from the study. Information such as hypotheses tested, parameters estimated, assumptions made, level of significance, experimental unit, and statistical model should be addressed. The number of animals used in the study should be justified in terms of the power of the study and pertinent considerations relevant to standard animal husbandry practices in the United States. Descriptions of the transformations (if any), calculations, or operations performed on the raw data should be provided, and the specific statistical methods used to analyze the raw data and separation of treatment means should be explained. Appropriate justification should be provided if any data points are excluded from analyses and reasons should be given if the statistical methods used differed from those initially planned in the study's protocol. Removal of data points based on numerical outlier analyses alone is not recommended and may impact determinations made from the review of a study report.

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**11. Results**

Describe the results of the study, whether favorable or unfavorable, including summary tables and diagrams of all relevant data recorded during the study. Each data table or summary diagram should be labeled so that the reader can understand the information provided in the data table or summary diagram. Summary results presented should show the treatment means using appropriate mean separation notations, following statistical analysis and mean separation.

**12. Discussion**

Include a discussion section, which is primarily used to interpret and explain study results, answer the question(s) for which the study was conducted, justify the study methods, and to critically and objectively evaluate the study results. In a narrative format, provide your interpretation of the study results and conclusions based on each of the treatment effects, interactions if any, or other observations in relation to the objective of the study.

**13. Relevant administrative and compliance items**

Provide a summary description of the procedures used to record, process, handle, and retain samples, raw data, and other study documentation. This includes descriptions of any protocol deviations and amendments, and an assessment of their impact on the outcome of the study, in addition to a description of circumstances that could have affected the quality or integrity of the data, specifying the time frame and the extent of their occurrence. Information on the occurrence of adverse events or lack of thereof, and any measures taken in response to an adverse event should be described in detail.

**14. Relevant additional information**

Include information such as amended study protocols, dates of monitor visits, audit certification, supplementary reports (such as statistical and analytical reports), copies of standard operating procedures (SOPs) or a summary narrative of information in the SOPs, or any other relevant additional information. Any additions, deletions, or corrections to the FSR should be included as an amendment, signed and dated by the FSR author(s).