November 12, 2013

Division of Dockets Management (HFA– 305),
U.S. Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Docket No. FDA– 2013–D–0928; Draft Guidance for Industry (GFI#221) on Recommendations for Preparation and Submission of Animal Food Additive Petitions;

Dear Docket Clerk:

The American Feed Industry Association (AFIA) and the National Grain and Feed Association (NGFA) appreciate the opportunity to comment on this draft guidance for industry (GFI #221) regarding "Recommendations for Preparation and Submission of Animal Food Additive Petitions" for our members. The U.S. feed industry has a long history of providing safe ingredients and animal feed for use domestically and abroad. Ingredient review processes that function efficiently are extremely important for the industry. To that end, we believe this draft guidance provides important information to make informed decisions on the correct ingredient approval path to pursue and to assist the industry in properly submitting a Food Additive Petition (FAP) for animal feed ingredients.

In general, our associations find this draft guidance document helpful in understanding the U.S. Food and Drug Administration's (FDA) requirements for information necessary for a successful FAP. We provide the following specific comments and recommendations on selected sections, which we believe would further enhance the information provided to the industry.

Section III. General Considerations and the FAP Process; C. Identity and Composition;
1. Identity

We believe the intent of the second paragraph in this section is unclear and should be clarified so as to provide better guidance on what information is desired by FDA. Accordingly, we offer the following suggestions.

- The terms "mixture" and "components" should be defined so that a clear understanding is provided to the industry.

- The first two sentences appear to be in conflict as to what is required when the substance is a mixture versus a component of a substance that is the subject of a FAP. We also believe the level of specified information should not be necessary in the identity section since it is required in the manufacturing section as detailed below.

- The term "material balance" is unclear even with the explanation provided by footnote 3. As such, we ask the agency to further clarify this term within the guidance.

- The guidance should provide some reference that establishes a reasonable threshold for the need to identify each component of a mixture. For example, does being "feasible to reasonably define" mean less than one percent, a specified parts per million level, any level within the limit of detection, or some other parameter?

The third paragraph in this section outlines information required if the food additive is of natural origin. The industry has experienced difficulty when submitting FAPs for a natural origin ingredient due to the variability of data. For example, natural origin ingredients may vary by geographical region, local weather conditions, degree of insect infestations (i.e. trauma to the plant causing it to react in a defensive manner with different ratios of constituents) and with different varieties, etc. Therefore, we request that FDA provide further clarification to address this issue. If such clarification is not provided, we believe that narrow specifications may unfairly preclude potential food additives from the market.

To provide additional clarification, we believe that information pertaining to the following issues would be useful:

- The level of detail that should be provided within the variability data.

- The level of detail that should be provided for genus and species. For example, if "wheat" was submitted to the FAP process, would all possible varieties need to be listed and detailed? Since wheat can be grown in many different locations (even some locations that may not be known or even thought about at the time of submission) and nutrient uptake (for example, selenium) can vary greatly in the different locations, how much of this information would need to be provided?

2. Manufacturing methods and control; a. Manufacturing process

In this section, FDA requests very detailed manufacturing information. We believe the agency needs to balance the information being requested to support the manufacturing methods and controls with the understanding that food additives are nonproprietary and the manufacturing process is not regulated, beyond the requirement that the marketed food additive is safe. We believe the level of detail requested by FDA within the draft guidance is unrealistic, inasmuch as a manufacturing process is not a regulatory requirement when manufacturing food additives that meet existing food additive regulations and ingredient specifications. Further, since manufacturing processes generally are proprietary to the company, we request that FDA detail in the guidance what information may be disclosed under the Freedom of Information Act.

Related to this concept, we also believe it is vitally important to encourage innovation in manufacturing; that is, one process should not be mandated by regulation to the exclusion of all others. Providing for innovation in the manufacturing process may result in a process that yields a product of higher quality and/or a more economical price, with the potential for the value and savings being passed on to the consumer.

Within the second paragraph of the section, the draft guidance states that all analytical methods used to monitor chemical reactions during manufacture are to be identified and described. We question whether this proposed criterion is required by regulation. In addition, what is the practical outcome if a method is

not developed? For instance, will a firm be required to change their method of manufacturing or develop a method?

At the end of the second paragraph, the draft guidance details that the submission should identify all alternative methods of manufacturing. We believe it is unclear what the agency desires with this request. For instance, does this request encompass all methods, regardless of their viability or usefulness to develop a product of high purity in an economical manner? If so, what approach would FDA find acceptable for a firm to use to discover the alternative manufacturing methods? For instance, what sort of evidence is required to indicate completion of this requirement, e.g., is a patent search or literature search required? As FDA is aware, many companies are researching the development of the same product. Therefore, it is very likely a competing company may have developed other methods which they consider proprietary and have not published. Finally, will these alternate methods also be reviewed as part of the submission?

Within the third paragraph of this section, FDA requests information regarding a complete description of the packaging process that will be used for the substance. We believe this requested information would represent a new and unnecessary requirement. We also do not believe that such information is required by regulation. In addition, we question why firms would need to validate packaging processes when most food additives would not yet be in production at the time of the submission.

2. Manufacturing methods and control; b. Batch preparation

Please see our comments pertaining to batch preparation within the Appendix section of this statement.

2. Manufacturing methods and control; c. Specifications for chemical identity and purity

In the first paragraph, the draft guidance contains a statement concerning "identifying and limiting any reaction byproducts or other impurities." We request that FDA clarify the statement by providing further detail as to the necessary threshold for identifying such substances. For instance, would the level of detection represent the necessary threshold? We assume that the principle of good manufacturing practices would apply in that FDA would expect that potential impurities be limited to the extent that it is economically feasible.

We also believe the language regarding the number of batches necessary is confusing, particularly since most food additives will not be in production at the time of submission. We recommend that FDA clarify how a firm should determine what would be a "significant number of pilot production batches?" For instance, can these be consecutive batches?

Further, we have confidentiality concerns with the level of raw data and statistical analysis of the data that FDA requests within a submission. The majority of this information likely is confidential since it reveals not just proprietary processes, but efficiencies of the operation. The submission of such information could provide competitors clues as to pricing of the substance, giving the competitor a possible unfair competitive advantage. We again request that FDA provide assurances as to how the agency intends to protect the confidential nature of this information.

2. Manufacturing methods and control; d. Food additive stability and mixability

In the first paragraph, we request that "production" be removed from the third sentence, since as expressed previously, all data submitted may not be from production batches.

Also in the first paragraph, the requirement for a firm to validate its analytical method to determine stability for every different animal food type that the food additive is intended for use could result in an endless matrix of types and variations. We recommend that a model of the most probable use be acceptable for determining stability in application testing.

Pertaining to the second paragraph, we strongly believe homogeneity in feed products should be the responsibility of the finished feed manufacturer, not the petitioner. Further, we believe such a homogeneity requirement is not supported by regulation.

A food additive manufacturer can provide recommendations to ensure homogeneity, however variances occur based on the equipment and actions of the finished feed manufacturer that are outside the control of the petitioner. We also believe the potential variations that would be associated with attempting to ensure homogeneity are essentially endless, given the many different feed manufacturing methods. For instance, each matrix may require extensive modification of the method of detection (including extraction process, recalibration of equipment and new impurities that need to be excluded). As such, we suggest that firms be allowed to use a model system in place of attempting to demonstrate homogeneity in every possible feed.

Based on industry's experience, FDA has been very specific in the types of studies that may be submitted for homogeneity and stability. However, this relevant and helpful information is not provided in the draft guidance. As such, we recommend that FDA include it within the final guidance.

D. Intended Use and Use Level, and Labeling; 1. Intended use and use level

As FDA notes in the first paragraph of this section, 21 C.F.R. § 571.1(c) requires that the FAP include "[d]ata establishing that the food additive will have the 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." In the second paragraph, FDA gives examples of the attributes of a food additive and cites to 21 C.F.R. § 170.3(o). *See* draft guidance – page 11, footnote 4. We believe the quality of FAPs will improve if the guidance more explicitly incorporates existing regulatory and statutory language regarding a food additive's attributes and intended effects. Consequently, we suggest the following minor revisions to page 11 of the draft guidance (with new language double underlined):

> The intended effect of the food additive should include one or more of the following attributes to the food: nutrient, aroma/flavor, taste, soluble or insoluble fiber, stabilization, emulsification, enzyme activity, sequestration, preservation, anti-oxidant activity, anti-microbial activity, nutritional or metabolic process activity, anti-caking, or another physical or technical functional effect, or effect on the structure or function of the body. [4] The FAP should specify the species, age and life stage of animals that will consume the food additive.

We also propose an amendment to footnote 4 that would read:

[4] 21 C.F.R. 170.3(o) provides a list of terms that describe physical or technical effects of types of food additives. Section 201(g)(1)(C). 21 U.S.C. § 321(g)(1)(C) defines a drug as, among other things, "articles (other than food) intended to affect the structure or any function of the body of man or other animals."

The above editorial changes incorporate more explicitly the language of 21 C.F.R. 170.3(o), which identifies terms that describe physical or technical effects of types of food additives. Inclusion of the statutory language from the definition of "drug," in section 201(g)(1)(C) of the FD&C Act clarifies that foods whose physical or technical effects are intended to affect the structure or function of the body are not drugs and so are appropriate subjects for FAPs.

Pertaining to the third paragraph, we offer the following suggestions:

- We do not believe FDA's intentions are clear when it uses the terms "tolerance" and "safety." We question whether the use of "residue level" would be more appropriate than "tolerance," and ask that the agency consider this revision. We also suggest that the guidance reference "Section H" for the requirements on tolerances for the food additive.

- We believe adding the words "by the target animal" at the end of the sentence in this paragraph better communicates that the higher tolerance is for the target animal.

E. Data Establishing the Intended Effect

We offer the following suggestions for data to establish intended effect:

- **Dose Level:** Within the draft guidance, FDA refers to dose level. We understand that in practice this requirement is not necessary for certain petitions. In response, we ask FDA to clarify those situations in which dose level is required. We also ask whether the agency intends to establish this as a new requirement for all animal food FAPs. If so, we further question the basis for such a requirement in regulation.

- **Intended Effect:** It also is our understanding that FDA currently requires one quality study to demonstrate the intended effect. We suggest this be stated in the guidance document in order to make it clear to the industry what is expected to meet this requirement so that informed decisions may be made regarding the approval processes and the necessary data requirements. In addition, we suggest that specific advice for study design also be included within the guidance.

- **Self-Limiting Uses:** We suggest that FDA provide further information regarding the type of required documentation associated with a "self-limiting use level." For instance, does FDA have expectations that such documentation include something more than palatability including, but not limited to, mechanical, product quality or stability? We believe the current language in the draft guidance is too open ended, and possibly could require exhaustive testing.

G. Safety Evaluation

We believe the last sentence of the opening paragraph pertaining to Good Laboratory Practice (GLP) study requirements is unclear concerning what is required regarding the conclusions under a non-GLP study. We suggest rewording the end of the sentence to be clearer in what is expected regarding the data from a non-GLP study and the food additive's safety. The revised end of the sentence would read:

> "…and explain how the conclusions have not been impacted regarding the food additive's safety."

G. Safety Evaluation; 1. Human food safety; c. Microbial food safety

In this subsection, we believe it is unclear whether this requirement is for all FAPs or only for FAPs that possess antimicrobial activity. It is our belief that this requirement is only for FAPs that have antimicrobial activity. Therefore, we suggest that in the second sentence the language regarding "all food additives" be replaced with "food additives with measurable antimicrobial activity" to make it clear when this information is necessary.

G. Safety Evaluation: 2. Target animal safety

We offer the following suggestions for guidance pertaining to safety evaluations:

- **Most Sensitive Life Stage and/or Species:** In the first paragraph, there is a reference to "…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."

  Pertaining to this guidance, FDA indicates the firm should consult with the agency to determine if the most sensitive life stage and/or species has been identified. We request FDA to provide clarity in the guidance to guide firms in their preparation of a submission to determine the appropriate sensitive life stage and/or species.

- **Use of Scientific Literature:** The statement in the sentence, "[Y]ou should use current scientific literature…" implies that only published studies may be used, and therefore the development process must be published in this search for a most sensitive species; and further, that the search for "most sensitive" be limited to target species. We respectfully suggest this wording be amended to indicate that scientific literature is not limited to only published literature and that in-house data can be used. The amended sentence would read:

  > "You may use current scientific literature and/or in-house data to identify the most sensitive life stage and/or species of the target species".

Appendix

We note for FDA that in the draft guidance, the Appendix is titled as "Appendix" and in the text of the guidance it is referred to as "Appendix 1." The titles should be made consistent.

Under item #9 within the Appendix, firms are to submit "all analytical control points and methods or process analytical controls used to monitor the [manufacturing] process." We note that for substances such as enzymes the specified criteria is identified for long time periods of time. As such, we question whether this level of detail is needed in the submission for all food additives.

Conclusion

AFIA and NGFA appreciate that FDA has published this draft guidance for industry. The comments within this statement represent our initial review of the information provided. As our member companies utilize the information to review and compile FAP submissions over the coming months, we will pass along any additional comments and clarifications that are identified to further strengthen this guidance document.

AFIA and NGFA appreciate FDA's consideration of our comments.

Sincerely,

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About AFIA:
The **American Feed Industry Association** (AFIA) is the world's largest organization devoted exclusively to representing the business, legislative and regulatory interests of the U.S. animal feed industry and its suppliers. AFIA also is the recognized leader on international industry developments. Members include more than 550 domestic and international companies and state, regional and national associations. These members manufacture over 75% of the nation's 165-million tons of feed annually. Member-companies are livestock feed and pet food manufacturers, integrators, pharmaceutical companies, ingredient suppliers, equipment manufacturers and companies which supply other products, services and supplies to feed manufacturers.

About NGFA:
The **National Grain and Feed Association** (NGFA), established in 1896, comprises more than 1,050 member companies that operate more than 7,000 facilities and handle more than 70 percent of the U.S. grain and oilseed crop. The NGFA's membership encompasses all sectors of the industry, including country, terminal and export grain elevators; commercial feed and feed ingredient manufacturers; biofuels producers; cash grain and feed merchants; end-users of grain and grain products, including processors, flour millers, and livestock and poultry integrators; commodity futures brokers and commission merchants; and allied industries that provide goods and services to the industry. The NGFA also consists of 26 affiliated State and Regional Grain and Feed Associations, and has strategic alliances with Pet Food Institute and the North American Export Grain Association.