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Guidance for Industry

Use of Nanomaterials in Food for Animals

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For further information regarding this document, contact Dragan Momcilovic, Center for Veterinary Medicine, Division of Animal Feeds (HFV-226), Food and Drug Administration, 7519 Standish Place, Rockville, MD 20855, 240-402-5944; email: dragan.momcilovic@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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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 Food and Drug Administration's (FDA's) current thinking regarding the use of nanomaterials or the application of nanotechnology in food for animals. It is intended to help industry and other stakeholders identify potential issues related to the safety or regulatory status of food for animals containing nanomaterials or otherwise involving the application of nanotechnology.

FDA's guidance documents, including this guidance, 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.

II. Scope

In this document, the term *animal food* means *food for animals*. This guidance is applicable to food ingredients that are intended for use in animal food and that (1) consist entirely of nanomaterials, (2) contain nanomaterials as a component, or (3) otherwise involve the application of nanotechnology.[1]

[1] In its evaluation of such materials, FDA intends to apply the principles outlined in the agency's guidance document entitled, "Considering Whether an FDA-Regulated Product Involves the Application of Nanotechnology," which is available online at: http://www.fda.gov/regulatoryinformation/guidances/ucm257698.htm. In addition, FDA issued a guidance related to the use of nanotechnology in food in June 2014 entitled, "Guidance for Industry: Assessing the Effects of Significant Manufacturing Process Changes, Including Emerging Technologies, on the Safety and Regulatory Status of Food Ingredients and Food Contact Substances, Including Food Ingredients that are Color Additives," which is available online at: http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/ucm300661.htm.

Medicated feed contains new animal drugs approved for use in or on animal food. This guidance does not apply to a nanomaterial form of a new animal drug or drug component (e.g., drug carrier) in medicated feed; however, it does apply to nanomaterial animal food ingredients in medicated feed.

This guidance is not intended to call into question the regulatory status of products that naturally exist in the nanoscale range or that contain incidental amounts of particles in the nanoscale range, and that have already been determined to be GRAS or approved in response to a food additive petition.

We are particularly interested in materials or end products that involve the application of nanotechnology to deliberately manipulate or control particle size in order to produce specific technical effects.

Materials or end products that naturally occur or naturally contain substances in the nanoscale range and are not further manipulated or engineered are not within the scope of this guidance. Examples of such substances include microorganisms or proteins that naturally exist at small scales.

We recognize that conventional manufacturing processes, such as milling or general combustion, may sometimes result in the animal food containing particles of varying sizes, including particles in the nanoscale range. This guidance is not intended to apply to the incidental presence of particles in the nanoscale range that may occur in animal food as a result of conventional manufacturing processes.

III. 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 or otherwise affecting the characteristics of any food[.]" Section 201(s) of the FD&C Act 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 (e.g., new animal drug, color additive, etc.).[2]

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

[2] 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; and (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).

section 409(a) of the FD&C Act (21 U.S.C. § 348(a)) and adulterated under section 402(a)(2)(C)(i) of the FD&C Act (21 U.S.C. § 342(a)(2)(C)(i)). In general, adulterated foods cannot be legally imported or marketed in the United States (21 U.S.C. § 331(a)). 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 (21 U.S.C. § 348(c)(1)(A)). 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, 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 (21 CFR 570.17).

Under section 201(s) of the FD&C Act, the use of a food substance may be shown to 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 based upon scientific procedures requires the same quantity and quality of scientific evidence as is needed for approval of a food additive petition (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. FDA's Center for Veterinary Medicine (CVM) is also accepting notifications of GRAS determinations for animal food substances through a pilot program.[3]

IV. Discussion

A. Nanotechnology and Food for Animals

Nanotechnology involves manipulation of materials on an atomic or molecular scale. It is an emerging technology that has the potential to be used across the spectrum of FDA-regulated products, including animal food.

FDA has not established regulatory definitions of "nanotechnology," "nanomaterial," "nanoscale," or other related terms. In June 2014, FDA issued a guidance for industry entitled, "Considering Whether an FDA-Regulated Product Involves the Application of Nanotechnology." As described in that guidance, at this time, when considering whether an FDA-regulated product involves the application of nanotechnology, FDA will ask: (1) whether a material or end product is engineered to have at least one external dimension, or an internal or surface structure, in the nanoscale range (approximately 1 nm to 100 nm) and (2) whether a material or end product is engineered to exhibit properties or phenomena, including physical or chemical properties or biological effects, that are attributable to its dimension(s), even if these dimensions fall outside the nanoscale range, up to one micrometer (1,000 nm).

[3] This program was announced in the Federal Register of June 4, 2010 (75 FR 31800). More information about the GRAS Notification Program for animal food is available online at: http://www.fda.gov/AnimalVeterinary/Products/AnimalFoodFeeds/GenerallyRecognizedasSafeGRASNotifications/default.htm.

These considerations apply broadly to all FDA-regulated products, including to food for animals.

The application of nanotechnology may result in product attributes that differ from those of conventionally-manufactured products, and thus may merit examination. However, FDA does not categorically judge all products containing nanomaterials or otherwise involving the application of nanotechnology as intrinsically benign or harmful. Rather, for nanotechnology-derived and conventionally-manufactured animal food products alike, FDA considers the characteristics of the finished product and its safety for its intended use. FDA's consideration of nanotechnology applications in animal food is consistent with the agency's guidance[4] and with the broader federal guidance on regulatory oversight of emerging technologies[5] and nanotechnology[6].

B. Physicochemical Properties of Nanomaterials in Food for Animals

Available scientific evidence indicates that materials manipulated on the nanoscale level through the use of nanotechnology may result in the materials possessing novel physicochemical properties. The physical characteristics of a particular nanomaterial, including increased surface area-to-volume ratio, morphology, surface features, and charge, can affect the biological behavior of the material.[7]

In addition, materials manipulated on the nanoscale level through the use of nanotechnology may affect the biodistribution, biocompatibility, or toxicity of the material.[8] For example, changing the particle size of a material may affect its absorption and transport in the body.[9] Thus, the bioavailability of a nanomaterial animal food ingredient may be significantly different from that seen or expected in a larger-scaled material with the same chemical composition, which may alter the minimum amount of the animal food ingredient necessary to achieve the intended technical or nutritional effect.

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[4] FDA issued guidance in June 2014 entitled, "Guidance for Industry. Considering Whether an FDA-Regulated Product Involves the Application of Nanotechnology." http://www.fda.gov/regulatoryinformation/guidances/ucm257698.htm

[5] The White House Emerging Technologies Interagency Policy Coordination Committee (ETIPC). 2011. Memorandum for the Heads of Executive Departments and Agencies: Principles for Regulation and Oversight of Emerging Technologies. http://www.whitehouse.gov/sites/default/files/omb/inforeg/for-agencies/Principles-for-Regulation-and-Oversight-of-Emerging-Technologies-new.pdf

[6] The White House Office of Science and Technology Policy (OSTP). 2011. Memorandum for the Heads of Executive Departments and Agencies: Policy Principles for the U.S. Decision-Making Concerning Regulation and Oversight of Applications of Nanotechnology and Nanomaterials. http://www.whitehouse.gov/sites/default/files/omb/inforeg/for-agencies/nanotechnology-regulation-and-oversight-principles.pdf

[7] FDA's Nanotechnology Task Force Report 2007 can be accessed at http://www.fda.gov/ScienceResearch/SpecialTopics/Nanotechnology/UCM2006659.htm

[8] Ibid.

[9] Ibid.

Similarly, two animal food ingredients of the same chemical composition, but of different particle size, shape, or other morphological feature, may exhibit different physicochemical properties. For example, some tea polyphenols are anti-oxidants in their bulk form, but the same tea polyphenols are pro-oxidants in their nanoscale form[10].

Because the application of nanotechnology may result in new or different physicochemical properties, specific data should be used as evidence to show that the use of the nanomaterial version of the animal food ingredient is safe for its intended use, even if it shares the same chemical composition as a larger-scaled animal food ingredient that is determined to be GRAS for that intended use or is a food additive approved for that intended use.

There are animal food ingredients that are approved as food additives or that are GRAS for their intended uses that could be manufactured to significantly alter their particle size or size distribution into the nanoscale range. In some instances, these changes could result in a material with different properties. In such cases, manufacturers should conduct safety assessments that are based on data and information relevant to the nanomaterial version and not rely entirely on the data and information used to determine the safety of a larger-scaled material with the same chemical composition.

C. Nanotechnology and GRAS Substances in Food for Animals

A determination that a particular use of a substance is GRAS (unless established by common use before 1958) requires both technical evidence of safety and a basis to conclude that this technical evidence of safety is generally known and accepted (i.e., general recognition of safety). At present, for nanotechnology applications in animal food, there are questions related to the technical evidence of safety as well as the general recognition of that safety that are likely to be sufficient to warrant formal premarket review and approval by FDA, rather than to satisfy criteria for GRAS status. When questions about the safety of the use of an animal food ingredient are raised and experts would need additional data that are not generally available to answer those questions, then the general recognition of safety criteria for GRAS status would not be satisfied for that use of that animal food ingredient. At this time, we are not aware of any animal food ingredient engineered on the nanometer scale for which there is generally available safety data sufficient to serve as the foundation for a determination that the use of such an animal food ingredient is GRAS.

Furthermore, where there is a lack of general recognition of the safety of a nanomaterial animal food ingredient for its intended use, it is likely that a GRAS notice for such a nanomaterial animal food ingredient would not meet the criteria of CVM's pilot GRAS notification program. Therefore, premarket review and approval of the animal food ingredient by FDA may be warranted. We recommend that you consult with us even if you believe that the generally available data and information could form a basis for a determination of GRAS status of an animal food substance that involves nanotechnology.

[10] Alotaibi, et al. 2013. Tea phenols in bulk and nanoparticle form modify DNA damage in human lymphocytes from colon cancer patients and healthy individuals treated in vitro with platinum-based chemotherapeutic drugs. *Nanomedicine* (Lond). Mar; 8(3):389-401.

V. Recommendations for Nanomaterial Animal Food Ingredient FAPs

Following a determination that an FAP is warranted, you should submit the FAP for your nanomaterial animal food ingredient to FDA. When developing a submission to the agency, please consult CVM Guidance for Industry (GFI) #221, "Recommendations for Preparation and Submission of Animal Food Additive Petitions." [11] CVM intends GFI #221 to provide guidance for meeting the FAP requirements established in 21 CFR part 571. The recommendations provided in GFI #221 apply generally to all food additives for animal food, including those that involve the use of nanotechnology.

When developing a submission for a FAP for a nanomaterial animal food additive, we recommend that you consider the following:

A. Identity

As with all other food additives, the FAP for a nanomaterial animal food additive must include information which identifies and characterizes the nanomaterial animal food additive. See section 409(b)(2) of the FD&C Act (21 U.S.C §348(b)(2)). The FAP must include the name and all pertinent information concerning the nanomaterial animal food additive, including chemical identity and composition of the food additive, its physical, chemical, and biological properties, and specifications prescribing the minimum content of the desired component(s) and identifying and limiting the reaction byproducts and other impurities (21 CFR 571.1(c)). Where such information is not available, a statement as to the reasons why it is not should be submitted.

The name of the nanomaterial animal food additive, like the name of a conventionally-scaled food additive, is identified in the relevant food additive regulation.

B. Manufacturing Methods and Controls

For any animal food additive, it may be important to provide information regarding the presence of byproducts and impurities associated with its manufacturing. Toxicity may be associated with byproducts and impurities resulting from the manufacture of a nanomaterial food ingredient. [12]

Nanomaterials may agglomerate or aggregate and interact with other ingredients in animal food matrices. FAPs involving nanomaterials should provide data on the stability of the nanomaterials in the proposed formulations and under the proposed conditions of use.

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[11] See GFI #221, "Recommendations for Preparation and Submission of Animal Food Additive Petitions." http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM367746.pdf

[12] J.J. Scott-Fordsmand, et al. 2008. The toxicity testing of double-walled nanotubes-contaminated food to *Eisenia veneta* earthworms. *Ecotoxicology and Environmental Safety 71 (2008) 616– 619.*

If a nanomaterial ingredient is intended to be distributed uniformly throughout an animal food matrix, then you should provide information demonstrating that the nanomaterial ingredient can be mixed to a uniform content in a representative animal food matrix.

The physicochemical properties of nanomaterials may change in liquid media. The effects of a particular liquid medium on the physicochemical properties of a nanomaterial animal food ingredient approved for use in dry animal foods are uncertain. For example, the stability of a nanomaterial animal food additive approved for use in dry animal foods may change when the same nanomaterial animal food additive is proposed for use in a liquid animal food. CVM generally will not assume a nanomaterial animal food additive approved for use in dry animal foods is safe nor has the same technical effect when used in liquid media. As a result, information related to changes in physicochemical properties may be needed to demonstrate safety or technical effect before an animal food additive, approved for use in dry animal food, is approved for use in a liquid medium.

C. Intended Use, Use Level, and Labeling

The regulations at 21 CFR parts 501 and 502 provide requirements for labeling and naming of animal foods and ingredients. In addition, FDA may require the label or labeling of an animal food additive, including a nanomaterial food additive for animal food, to include any information necessary to ensure the safe use of the food additive. See section 409(c)(1)(A) of the FD&C Act (21 U.S.C §348(c)(1)(A) and 21 CFR 571.100(a)). Foods that do not bear such required labeling may be deemed misbranded under sections 403 and 201(n) of the FD&C Act.

D. Analytical Methods

Scientifically valid analytical methods that are capable of determining the chemical composition and the amount of the nanomaterial animal food additive contained in various animal food matrices should be used. The analytical methods should correctly identify the nanomaterial animal food ingredient by its relevant physical properties (e.g., 3-dimensional properties such as size and/or shape).

Complexities of detection and characterization of nanomaterials pose particular challenges to analytical methods. A detailed description of the analytical methods used to determine the identity, purity, quality, and strength of the nanomaterial animal food additive should be provided. Such analytical methods should be described in sufficient detail and specificity as to permit the reviewer to determine the validity of the methods to verify the purity, quality, and strength of the nanomaterial animal food additive. Analytical methods may need to be performed as the animal food additive is produced, after it is purified, in its marketed packaged matrix, and in a representative animal food matrix.

E. Safety Evaluation and Proposed Tolerances for the Food Additive

As part of the FAP process, FDA examines safety data provided by the petitioner to show whether the food additive will be safe for its intended use. Both human food safety and target animal safety must be addressed in any FAP for a substance intended for use in food for animals that are raised for food production. See 21 CFR part 571. As with all other food additives, these two sections of an FAP for nanomaterial animal food additives should contain the scientific data necessary to demonstrate the safety of the nanomaterial animal food additive for humans and target animals under the conditions of intended use.

The information needed to demonstrate human food safety for a nanomaterial animal food additive may differ from that needed for a larger-scaled material with the same chemical composition. For example, you may need to provide a specially designed assay (see "Analytical Methods" above) to characterize the distribution and accumulation of the nanomaterial in the edible tissues (including milk and eggs) derived from food-producing animals.

The information needed for demonstrating target animal safety for a nanomaterial animal food additive may differ from that needed for larger-scaled material with the same chemical composition. For example, if the bioavailability of a nanomaterial animal food ingredient differs from its larger-scaled counterpart, then the toxicological profile for the larger-scaled counterpart may not be adequate to ensure the target animal safety of the nanomaterial animal food additive. In this example, you may need to provide a toxicological profile that is specific for the nanomaterial animal food additive for its proposed use.

F. Proposed Regulation

The proposed regulation section of an animal food additive petition should include information, including technical specifications, that is necessary for proper identification of the nanomaterial animal food additive. If applicable, the proposed regulation should have proposed limitations on the conditions of use to ensure safety.

G. Environmental Assessment

The potential adverse environmental impact of a nanomaterial may differ from that of a larger-scaled material with the same chemical composition. Impact on the environment may occur at various stages of the ingredient's life cycle, including manufacture, storage, use, and disposal. We recommend contacting CVM[13] early in product development to determine whether the approval of a FAP for the nanomaterial animal food additive would qualify for a categorical exclusion, or if it would not qualify for a categorical exclusion, to determine the appropriate scope of an environmental assessment.

[13]See contact information on title page.

VI. Conclusion

We recommend that you contact CVM early in the product development process so that a determination can be made as to whether your animal food product involves the application of nanotechnology and so that any questions related to safety and regulatory status can be appropriately addressed. To facilitate the efficient development and approval of FAPs for nanomaterial animal food additives, CVM encourages pre-petition consultations with our Division of Animal Feeds.