Food Allergen Labeling Exemption Petitions and Notifications:
Guidance for Industry

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U.S. Department of Health and Human Services
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I. Introduction

This document describes the data that FDA's Center for Food Safety and Applied Nutrition (CFSAN or "we") will consider when evaluating petitions and notifications seeking exemptions from the labeling requirements of section 403(w)(1) of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) regarding ingredients derived from major food allergens.

This guidance is intended to address the relevant issues for most submitters[1], but some recommendations may not be applicable in all cases. If a recommendation does not appear to apply to a particular ingredient or use, the submitter should explain briefly why the scientific evidence recommended here is not needed for that ingredient or use. We also encourage potential submitters to consult us before submission to discuss any questions or data needs.

Information on allergen labeling requirements for conventional foods and dietary supplements can be found at http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/Allergens/default.htm.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidance documents describe our 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 FDA guidance means that something is suggested or recommended, but not required.

II. Statutory Authority

[1] We use the term submitters to mean any party who submits a petition or notification seeking an exemption from the labeling requirements for major food allergens.

The Food Allergen Labeling and Consumer Protection Act of 2004 (FALCPA) (Title II of Public Law 108-282) amended the FD&C Act by defining the term "major food allergen" and stating that foods regulated under the FD&C Act are misbranded unless they declare the presence of each major food allergen on the product label using the common or usual name of that major food allergen. Section 201(qq) of the FD&C Act (21 U.S.C. 321(qq)) now defines a major food allergen as "[m]ilk, egg, fish (e.g., bass, flounder, or cod), Crustacean shellfish (e.g., crab, lobster, or shrimp), tree nuts (e.g., almonds, pecans, or walnuts), wheat, peanuts, and soybeans" and also as a food ingredient that contains protein derived from these foods. The definition excludes any highly refined oil derived from a major food allergen and any ingredient derived from such highly refined oil.

In some cases, the production of an ingredient derived from a major food allergen may alter or eliminate the allergenic proteins in that derived ingredient to such an extent that it does not contain allergenic protein. In addition, a major food allergen may be used as an ingredient or as a component of an ingredient such that the level of allergenic protein in finished food products does not cause an allergic response that poses a risk to human health. Therefore, FALCPA provides two mechanisms through which such ingredients may become exempt from the labeling requirement of section 403(w)(1) of the FD&C Act. An ingredient may obtain an exemption through submission and approval of a petition containing scientific evidence that demonstrates that the ingredient "does not cause an allergic response that poses a risk to human health" (section 403(w)(6) of the FD&C Act). This section also states that "the burden shall be on the petitioner to provide scientific evidence (including the analytical method used to produce the evidence) that demonstrates that such food ingredient, as derived by the method specified in the petition, does not cause an allergic response that poses a risk to human health." Alternately, an ingredient may become exempt through submission of a notification containing scientific evidence showing that the ingredient "does not contain allergenic protein" or that there has been a previous determination through a premarket approval process under section 409 of the FD&C Act that the ingredient "does not cause an allergic response that poses a risk to human health" (section 403(w)(7) of the FD&C Act).

To evaluate these petitions and notifications, we will consider scientific evidence that describes-

1. The identity or composition of the ingredient;
2. The methods used to produce the ingredient;
3. The methods used to characterize the ingredient;
4. The intended use of the ingredient in food; and

5a. For a petition, data and information, including the expected level of consumer exposure to the ingredient, that demonstrate that the ingredient when manufactured and used as described does not cause an allergic response that poses a risk to human health; or

5b. For a notification, data and information that demonstrate that the ingredient when manufactured as described does not contain allergenic protein, or documentation of a previous determination under a process pursuant to section 409 of the FD&C Act that the ingredient does not cause an allergic response that poses a risk to human health.

We will evaluate this scientific evidence only for the specific ingredient and specific use(s) identified in the submission.

FDA recognizes that there are several methods that can be used to de~~termine~~monstrate that an ingredient meets the ~~safety~~ standards in 403(w)(6) and 403(w)(7) of the FD&C Act. Each submitter may determine which approach is most appropriate for the specific ingredient and specific use(s) identified in the submission.

III. Recommendations for Preparing Submissions.

A. Determining Need for Submission

The following points should be considered in determining whether to submit a petition or notification:

- An ingredient derived from a major food allergen that does not contain protein is not subject to the labeling requirements described in section 403(w)(1) of the FD&C Act. We are aware that ~~a limited number of~~there are some technologies (e.g., distillation) that may be able to produce protein-free ingredients because of the nature of the process and fundamental biochemical properties of proteins, peptides, and amino acids. When other technologies are used to produce an ingredient, information and expertise available to the manufacturer ~~remains responsible~~ ~~will~~should make it possible to identify and apply the ~~for using~~ appropriate analytic methods to ensure that the ingredient does not contain protein. The methods used should be shown to be sufficiently accurate and sensitive under the conditions of use, including consideration of extraction efficiencies and possible interferences, should be scientifically appropriate, and sufficiently sensitive to demonstrate that no proteins or peptide fragments are present in the ingredient. Manufacturers should also consider potential batch to batch variation in the composition of the ingredient. Manufacturers may discuss methodological issues with us.

- A petition should be used to demonstrate that an ingredient derived from a major food allergen that may contain allergenic proteins, or derivatives of allergenic proteins such as peptide fragments, does not cause an allergic response that poses a risk to human health in food allergic individuals.

- A notification should be used to demonstrate that an ingredient that may contain proteins or protein fragments derived from a major food allergen does not contain allergenic protein.

B. General

Each submission should contain information identifying the organization and individual primarily responsible for the submission. This should include the name of the individual and organization, a complete mailing address, a physical address if this differs from the mailing address, phone and fax numbers, and an electronic mail (email) address for the organization and

for a primary contact. A joint submission from several organizations should include complete information for each organization.

C. Ingredient Description

For the purposes of this guidance document, ~~we consider an~~ ingredient~~s~~ ~~to be any substance that is intentionally added to food. This~~ include~~s~~ substances that are-

- Derived (e.g., through chemical, biochemical, mechanical, fermentation or bioengineering processes) from a major food allergen and that contain proteins or peptides; or

~~Organisms, enzymes, or other complex mixtures that are grown or prepared using one or more of the major food allergens.~~

A submission should provide a complete description of the ingredient including-

- Name – Both the common or usual name and any scientific name(s) of the ingredient;
- Source – The major food allergen source of the ingredient, if this is not obvious from the name, or the major food allergen sources used in the manufacture or engineering of the ingredient;
- Properties – The chemical and biological properties or characteristics of the ingredient including molecular structure, sequence, etc., as appropriate;
- Standards – Any existing food standards of identity or specifications for the ingredient, such as from the FDA's food standards of identity regulations, Food Chemicals Codex, or Codex Alimentarius; and
- Composition - The composition of the ingredient, including the methods used to determine composition, and batch-to-batch variation in composition should be described. If the ingredient contains more than one component, all components, including non-allergens, (including carriers or diluents), as well as the relative proportion of each in the ingredient should be described.

D. Ingredient Preparation or Manufacture

The method(s) or procedure(s) used to prepare or manufacture the ingredient should be described completely, particularly those steps that alter the amount, relative composition, or biochemical state of the proteins present. This description should include, for example-

- Physical treatments – such as grinding, pressing, filtration;
- Temperature treatments – such as heating, cooking, baking, retorting;
- Chemical treatments – such as solvent extraction, hydrolysis (both enzymatic and non-enzymatic), cross-linking;
- Growth conditions (if relevant) – such as the composition of the growth or nutrient media used in the manufacture of enzymes or organisms; and/or
- Bioengineering process (if relevant) – such as details of the construct, transformation event, and DNA and amino acid sequences.

The description of the manufacturing or preparation process should include-

- The conditions used at each step in manufacturing or preparation from raw material to the final ingredient. This should include (as applicable) a full description of time, temperature, pH, pressure, volume, and acceptable range for each;
- Information on how process conditions are monitored and controlled at each step;
- A description of any testing that is done to measure or characterize proteins or peptides in the ingredient during or after processing (including quality assurance testing and information describing the validation of these tests); and
- Statistics on batch-to-batch variations in ingredient characteristics, particularly those related to protein content, identity, and structure.

E. Ingredient Protein Characterization

The submission should provide a chemical and biological characterization of the ingredient, including details of the methods used for analysis of the ingredient, particularly for the proteins or peptides in the ingredient. For ingredients that are or that contain peptide fragments, this should include information on the distribution of peptide fragment sizes and whether these peptide fragments are large enough to be immunologically-relevant. This should include-

- The amount of total protein or peptide present, including information on the method(s) used to measure these proteins or peptides;
- Characterization of the proteins or peptides, including -
    - The number (and range) and sizes (molecular weight or amino acid length) of the proteins and peptides; and
    - The biochemical characteristics of these proteins and peptides (including sequences if known), and the methods used to determine these characteristics. The description of the methods used should include sufficient information to evaluate the precision and accuracy of the method;
- Batch-to-batch variation in the amounts and characteristics of the proteins and peptides from analysis of multiple batches of the ingredient; and
- The amount and molecular characteristics of allergenic protein or peptides present (if possible), including a description of the method used to determine these characteristics.

F. Ingredient Application

To help us evaluate potential consumer exposure, the submission should describe the intended use (or uses) of the ingredient in the final food product(s). This should include-

- Intended use level for each food or food application;
- Information on variations from the intended level that occur normally during manufacture of the final food product(s);
- Information on any technical effects that limit the maximum amount of the ingredient that can be used;
- Information on the method of incorporation of the ingredient into foods (if relevant); and

- Information on any methods that are (or can be) used to measure the amount of the ingredient in foods.

G. Methods

Our ability to evaluate the scientific evidence in a submission can be affected by the extent to which the submission describes the methods used to obtain that evidence and an understanding of how these methods were validated. Therefore, for each analytical method used to characterize the ingredient, we recommend that a submission describe-

- The method as used, including the sources of any test kits, special reagents, and analytical equipment;
- The rationale for using a particular method, including a discussion of the benefits and limitations of the particular method;
- The process used to validate the method for use with the specific ingredient or food. Note that the use of internal kit standards or simple spiking procedures are generally not sufficient to validate that a method is performing as intended and that there are no interferences (either positive or negative);
- The recovery and/or extraction efficiency of the assay when used with the specific ingredient or food;
- The Limit of Detection (LOD), Limit of Quantitation (LOQ), and precision of the assay (if applicable);
- The sampling plan used – describing how samples were taken, how many were analyzed; and
- The statistics of the sampling results – such as the mean and standard deviation.

Enzyme-linked immunosorbent assay (ELISA)-based methods are the most widely used methods for detecting or measuring food allergens. However, given the limitations of ELISA-based methods, submitters should consider using additional analytical methods, such as using polymerase chain reaction (PCR) or mass spectrometry, to supplement data obtained using ELISA assays.

H. Environmental Assessment

Under 21 CFR part 25, all applications or petitions requesting agency action require the preparation of an environmental assessment or a claim of categorical exclusion. Please contact FDA for further information related to the FDA's regulations in 21 CFR part 25 regarding the procedural provisions under the National Environmental Policy Act of 1969.

IV. Additional Information for Petitions

A petition for a labeling exemption must contain scientific evidence showing that the ingredient does not cause an allergic response that poses a risk to human health under section 403 of the FD&C Act. Appendix 1 contains a detailed discussion of FDA's thinking on what constitutes an allergic response that poses a risk to human health. In general, we consider any of the possible objective allergic reactions as an "allergic response that poses a risk to human health" in

evaluating the scientific evidence presented in petitions requesting labeling exemptions for specific ingredients. In addition, subjective reactions that are associated with objective reactions at higher doses or that are of sufficient severity to stop a dose escalation study also may be considered allergic responses that pose a risk to human health. If subjective reactions were observed or recorded in a clinical study, we recommend that the petition include a discussion of how those data were used, or why they were not used. There are two types of scientific evidence that can generally be used, along with consumer exposure data, to demonstrate this: clinical testing (either *in vivo* or *in vitro*) and risk modeling.

A. Consumer Exposure

Risk for food allergic individuals is a function of multiple factors. The factors that are relevant for evaluating petitions are the amount of allergenic protein present in a food and the amount of that food consumed in a single eating occasion. Therefore, a petition should include information on the expected consumer exposure from consumption of the final food product(s) containing the ingredient. We suggest that this information include-

- Information on actual consumption levels for each intended food or food use at the mid-range, and at the 90% and 95% levels for consumers of that food;
- For ingredients that might be used in multiple foods, an estimated integrated consumption level at a single eating occasion (such as a complete meal); and
- Information on differential consumption patterns for consumers of different ages, genders, or ethnicity.

If necessary, the submitter should consider several different consumption scenarios to address various consumption patterns such as different consumption patterns in children and adults for some foods or different exposure levels from multiple uses of an ingredient.

B. Clinical Testing – Oral Provocation Studies

Clinical testing by oral food challenge of food allergic individuals is the most reliable way to assess the ability of a food or ingredient to provoke an allergic response in food allergic individuals. The double-blind, placebo-controlled food challenge is considered to be the best format for an oral challenge but single blind or open challenges may also be appropriate depending on the nature of the product and the food allergic individuals involved.

Regardless of the specific format used, we emphasize that to the extent possible the patient population involved should be ~~representative of the sensitive population~~fully described ~~as a whole~~, that each patient challenged be ~~fully~~ characterized, and that the form, dosing, and delivery system for the test material be appropriate. Studies that fail to address one or more of these points are less able to demonstrate that the ingredient does not cause an allergic response that poses a risk to human health. Data describing the result of oral food challenges should include:

- Information on the individuals challenged, such as-
    - The number of individuals enrolled and challenged in each study;

- All available clinical ~~description of~~information for each individual challenged [e.g., age, gender, nationality/ race, skin prick test or *in vitro* immunoglobulin E (IgE; the class of antibodies involved in allergic reactions) results if these are available, medical history, history of food allergic disease (e.g., frequency and severity of prior reactions), co-morbidities] and any medications that were used during the challenge; and
- Information supporting that, at the time of testing, all individuals challenged were allergic to the major food allergen that was the source of the ingredient and that they represent the range of sensitivities in the allergic population for that major food allergen.

- Information on the clinical protocol used, such as-
  - A description of the subject recruitment and randomization procedures;
  - Relevant inclusion and exclusion criteria for subject selection;
  - A description of the clinical primary endpoints;
  - A description of the material used in the challenge, including form and preparation of the material, and (if available) information on the relative concentration and distributions of allergenic proteins in the test material;
  - The carrier or matrix used;
  - The dosing pattern used, including-
    - All dose levels administered;
    - The time intervals between administered doses;
    - A description of how each dose is quantified (for example, as amount of whole food, amount of the specific ingredient, or amount of protein);
    - An indication of whether each dose level is reported as a discrete or cumulative dose; and
    - Information on how and when the placebos (if any) were administered;
  - A description of how responses were reported or measured, including-
    - The clinical criteria used, including information on whether both subjective and objective responses were recorded; and
    - Information on whether the severity of the response was measured, and if so how severity was classified;
- A complete statistical analysis of the results (based on study subject number and clinical endpoints); and
- A description of any other factors that we should consider when interpreting the results.

The National Institutes of Health, National Institute of Allergy and Infectious Diseases sponsored an expert panel that published "Guidelines for the Diagnosis and Management of Food Allergy in the United States: Report of the NIAID-Sponsored Expert Panel." The guidelines include the expert panel's recommendations and overall discussion of the use of oral challenge studies, including the rationale for using oral challenge studies, and the potential benefits and harms. (http://www.niaid.nih.gov/topics/foodallergy/clinical/Pages/default.aspx). The European Academy of Allergy and Clinical Immunology has published similar guidelines. (http://www.eaaci.org/attachments/EAACI-%20Food%20Allergy%20Management%20&%20Diagnosis.pdf).

Note that we expect all clinical studies involving human subjects submitted in support of a petition to be carried out in conformance with the FDA Human Subject Protection Regulations (http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/ucm155713.htm) or equivalent protection and standards including Good Clinical Practice (GCP[2]) in the country where the studies were conducted.

C. Clinical Testing – Skin Prick, *In Vitro* and Other Studies

The ability of an ingredient to cause an allergic response in food allergic individuals can also be assessed using diagnostic procedures such as skin prick tests or by *in vitro* testing using sera from food allergic individuals to assess whether IgE from these individuals will bind to proteins and peptides in the ingredient. There are several forms of *in vitro* assay that can be used to characterize the interaction between sera from allergic individuals and the proteins in food ingredients. Depending on the format of the assay used, such studies can produce information on which proteins in the food are recognized by antibodies from allergic individuals, on immunologic relationships between foods or proteins, on the levels of IgE antibodies in individual sera, and on the kinetics of antigen-antibody interactions. By comparing antibody binding properties of the ingredient in the petition (or from proteins contained in that ingredient) to the antibody binding properties of the source major food allergen, it may be possible to demonstrate that the ingredient will not cause allergic responses.

Regardless of the specific testing format used, we encourage submitters to test a statistically significant number of well characterized food allergic individuals. Appropriate procedures should be used to ensure that any interfering medications have been withdrawn for an appropriate period, that no confounding conditions are present (particularly for skin prick testing), and that appropriate positive and negative controls (such as histamine and saline for skin prick tests) are used. Each *in vitro* assay should be validated and fully controlled and data from all tests should be presented. Because food allergic individuals may be sensitive to different sets of specific proteins in a major food allergen, we encourage submitters to report results from testing each serum individually.

The data describing the results for each method should include-

- The number of test subjects and individual sera used;
- The criteria used for selecting test and control subjects and sera, including any relevant inclusion or exclusion criteria;
- Information on each subject or serum donor [e.g., age, gender, nationality/ race, medical history, history of food allergic disease (e.g., frequency and severity of prior reactions, co-morbidities, etc.), current medications during the challenge]. It is critical that sufficient data be provided to demonstrate that all individuals tested or donating test sera are allergic to the major food allergen that was the source of the ingredient and that they

[2] GCP is a standard for designing, conducting, recording and reporting trials that involve the participation of human subjects. See the web page "Running Clinical Trials" on the FDA web site for more information. (http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/default.htm)

are representative of the allergic population for that major food allergen and that all control individuals or donors of sera are not allergic to the major food allergen;
- For skin prick testing, a detailed description of the testing procedure used (e.g., the testing apparatus and method – i.e., prick, etc., where the extracts were placed on the skin, how skin test results were clinically assessed by wheal size and/or flare, etc.) as well as all positive and negative control procedures and the criteria used to determine whether there was a positive response;
- For *in vitro* serum testing, a detailed description of the assay procedure or procedures used (e.g., Western blot, ELISA), including all internal controls and validations;
- Complete characterization of all materials tested, particularly if extracts or derivatives of whole foods or ingredients are used, including a description of the procedures used to prepare the test material. This information should be sufficient to demonstrate that the test material is representative of the ingredient or of the proteins and protein derivatives contained in the ingredient;
- A complete description of the results and of the data analysis, including statistical analysis; and
- A discussion of the limitations of the data submitted.

New methods for assessing allergenicity and allergen-specific IgE-mediated responses are being developed. Until such methods have been fully validated, we recommend that they only be used as supporting data in conjunction with either skin prick or *in vitro* serum testing.

D. Risk-Based Methods

Absent direct clinical or challenge data, a submitter may be able to demonstrate that an ingredient will not cause an allergic response that poses a risk to human health by risk modeling using data on consumer exposure to the ingredient and published data on the distribution of minimal eliciting doses in the sensitive population. Previously, FDA determined that this modeling could be done using either a risk assessment or safety assessment-based approach (Approaches to Establish Thresholds for Major Food Allergens and for Gluten in Food, 2006) (Threshold Report). FDA also determined that the risk assessment-based approach is more transparent and scientifically rigorous than the safety assessment-based approach, and should be used when sufficient data are available. For either the risk assessment-based or safety assessment-based approach, we encourage pre-submission consultation with FDA.

Risk Assessment-Based Approach
The risk assessment-based approach combines data on the distribution of minimal eliciting doses in the entire food allergic population with data on consumption and exposure to estimate the probability that a food allergic individual will experience an allergic response. This approach allows analysis of different consumption scenarios as well as consideration of special populations. One major advantage of the risk assessment-based approach is that it provides explicit information on the uncertainties associated with the reaction probabilities.

If risk assessment-based modeling is used, the petition should describe-

- The clinical data used to model the distribution of sensitivities to the major food allergen in the food allergic population. This should include citation of published data and submission of any unpublished data used. These data should include a complete description of how the clinical studies were conducted;
- The statistical techniques used to develop the dose distribution model (or models) and of all the statistical and model uncertainties. If possible, the petition also should describe the effect of using alternate modeling approaches;
- The data and statistical techniques used to model the distribution of the major food allergen in finished foods that incorporate the ingredient;
- The data uncertainties, including the uncertainties associated with combining data from different challenge studies (if relevant), the effects of factors used to exclude individuals from the studies;
- The data and statistical techniques used to model consumption of the final food by food allergic individuals. If consumption patterns differ between subpopulations (such as between adults and children), the petition should model each subpopulation independently;
- The models and procedures used to estimate the probability of allergic responses by food allergic individuals;
- The results of the modeling, including all ranges and uncertainties; and
- How these results demonstrate that the ingredient does not cause an allergic response that poses a risk to human health.

Safety Assessment-Based Analysis

If sufficient data are not available for risk assessment modeling, it may be possible to assess whether an ingredient will cause an allergic response that poses a risk to human health by using a safety assessment-based analysis. A safety assessment-based analysis uses the Lowest Observed Adverse Event Level (LOAEL) or No Observed Adverse Event Level (NOAEL) for the most sensitive individual in the food allergic population and one or more uncertainty factors to estimate an exposure level that is unlikely to cause an allergic response in food allergic individuals. This level can be compared to expected actual consumption of the ingredient to estimate expected risk. Because a safety assessment does not consider the entire food allergic population, this type of analysis will be most appropriate in situations where the clinical testing data are very limited or indirect.

If a safety assessment is used, the petition should describe-

- The clinical data used to estimate the LOAEL and NOAEL in the food allergic population. This should include all pertinent information on the methodologies of the challenge studies used to identify these levels as well as all citations of published data and descriptions of any unpublished data used. The studies used to generate these data should meet the criteria described for direct clinical testing of the ingredient;
- How the LOAEL and NOAEL were determined based on the clinical data. In particular, we suggest that the petition describe all types of responses, e.g., subjective or objective, noted in the challenge data and how the submitter considered the responses in determining the LOAEL and/or NOAEL;

- The uncertainty factors that the submitter applied and the rationale for these factors. This discussion should include a description of the uncertainties associated with small data sets or with extrapolation from indirect data. Other factors to consider include uncertainties associated with comparing data from different challenge studies, exclusion of sensitive populations; and
- How these results demonstrate that the ingredient does not cause an allergic response that poses a risk to human health.

E. Other data

The petition may include additional relevant information, such as from animal testing (see Appendix 2), clinical case reports, or *in vitro* studies. If additional information is included, we recommend that the submitter describe how it generated or obtained the additional information. For laboratory studies, this should include a complete description of study methods and controls and of how the results were analyzed.

V. Additional Information for Notifications

Under section 403 of the FD&C Act, a notification for a labeling exemption must contain scientific evidence showing that the ingredient does not contain allergenic protein *or* that that there has been a previous determination through a premarket approval process under section 409 of the FD&C Act that the ingredient does not cause an allergic response that poses a risk to human health. In the latter case, as part of the premarket approval process, we will work with the submitter regarding the process for submitting a notification under section 403(w)(7)(A)(ii) of the FD&C Act.

A. Protein Characterization.

To demonstrate that a protein-containing ingredient does not contain allergenic protein, the notification should include a complete characterization of the protein (or proteins) and peptides that are present in the ingredient. This includes the information described in "Ingredient Protein Characterization" above (Section III.E of this document). In addition, the notification should contain evidence that the protein (or proteins) or peptides present are not allergenic. In some cases, where the original major food allergen is known to have only one or a few well characterized allergenic proteins, this can be done by demonstrating that the protein or peptides in the ingredient are different from the known allergenic proteins. However, because each allergic individual may be sensitive to different proteins in a food, in most cases we recommend that submitters use either *in vivo* or *in vitro* clinical data (as described above for a petition) to demonstrate that the ingredient does not contain allergenic protein.

B. Other data

The notification may include additional relevant information, such as from animal testing (see Appendix 2), clinical case reports, or *in vitro* studies. If additional information is included, we

recommend that the submitter provide a complete description of how it was generated or obtained. Laboratory studies should include a complete description of study methods and controls and of how the results were analyzed.

VI. Appendices

Appendix 1 Allergic Responses that Pose a Risk to Human Health

FDA considers the terms "allergic response" and "allergic reaction" to be equivalent for the purpose of this guidance. To help us determine what scientific evidence is needed to demonstrate that a food ingredient does not cause an allergic response that poses a risk to human health, we have reviewed the available scientific literature on food allergic responses and response severity.

We have defined food allergy as an IgE-mediated hypersensitivity to food (see Threshold Report). Although non-IgE-mediated, mixed, and cell-mediated reactions have adverse health consequences, only IgE-mediated mechanisms have the potential to cause acute life-threatening reactions. Further, IgE antibody-mediated reactions are the most common and of the greatest public health concern. Therefore, we will continue to consider only IgE-mediated allergic responses as relevant to these petitions and notifications while noting that the labeling and exemption standards developed using this consideration will also be protective of food allergic individuals who experience other immune-mediated adverse reactions to foods.

IgE-mediated responses are the result of a two-step process – sensitization and elicitation. Sensitization generates IgE antibodies that recognize specific proteins in food allergens. These IgE antibodies bind to receptors on the surface of mediator cells lining various mucosal membranes of the body. If an individual does not encounter a food allergen after becoming sensitized to that food allergen, there is no further biological response. However, when an individual does encounter the food allergen that is recognized by the IgE antibodies, and sufficient protein is present, the protein interacts with, and cross-links, the IgE antibody-bound cell receptors. This leads to the cellular release of inflammatory mediators responsible for the signs and symptoms of an allergic reaction. Although the manifestation of an "allergic response" requires both sensitization and elicitation, allergen labeling under section 403(w)(1) of the FD&C Act is intended to protect the health of individuals who have food-specific allergies, i.e., those who have previously been sensitized. Therefore, we consider allergic responses to be elicitation of IgE-mediated release of inflammatory mediators in food allergic individuals.

IgE-mediated allergic reactions can occur within a few minutes to hours after a food allergic individual consumes a food allergen. The reactions can result in a wide range of signs and symptoms, ranging from mild, reversible irritation to severe, life-threatening respiratory distress and shock. Allergic reactions may involve a single organ system or multiple systems. Specific organ systems include the skin (e.g., pruritis, erythema, urticaria, angioedema, eczema), eyes (e.g., conjunctivitis, periorbital swelling), nose (e.g., rhinitis, sneezing), oral cavity (e.g., swelling and itching of lips, tongue, or palate), or gastrointestinal tract (e.g., reflux, colic, abdominal pain, nausea, vomiting, diarrhea). In severe reactions, the "shock organs" of the respiratory tract (e.g., cough, asthma, difficulty breathing, swelling around the larynx and vocal cords) and cardiovascular system (e.g., faintness, hypotension) are involved. This can lead to loss of consciousness, asphyxiation, shock, or death.

An allergic reaction can produce responses that are subjective, objective, or both. Subjective symptoms (e.g., mild nausea, itching, or gastrointestinal discomfort) are those that are

experienced by the affected individual but that cannot be confirmed by an observer. Objective signs (e.g., urticaria, vomiting, or wheezing) are those that can be observed by other individuals. Subjective symptoms may be precursors of objective signs.

The signs and symptoms of an allergic reaction vary from one individual to another and may also vary for the same individual on different occasions. Further, any individual sign or symptom may vary in intensity or duration. For example, an allergic reaction might be manifested as a few small hives or as multiple large hives that cover most of the torso. Reactions may subside spontaneously or progress in both the number of organ systems involved and severity. Reactions that have a rapid onset and that involve multiple organ systems are generally considered to be anaphylaxis. However, anaphylaxis may also present with a delayed and protracted course involving only one organ system.

It is not known what determines the severity of an allergic reaction. It is likely that several factors including individual sensitivity, the amount and characteristics of the food consumed, underlying co-morbid conditions (e.g. asthma), and the effects of other foods and drugs all interact to determine the course and severity of each allergic reaction. There is evidence that some of the major food allergens (e.g., peanuts and tree nuts) are more likely to trigger severe reactions than others (e.g., wheat). It is known that individual sensitivity varies over a wide range in the food allergic population.

The FDA Allergen Threshold Working Group (Working Group) has previously considered the meaning of the phrase "allergic response that poses a risk to human health" in the report "Approaches to Establish Thresholds for Major Food Allergens and for Gluten in Food" (2006). At that time, the Working Group noted the lack of consensus on the applicability of subjective symptoms as biomarkers for severe allergic reactions and the very limited published data on subjective symptoms in clinical trials. The Working Group also noted that there is a broad consensus that ~~all~~ any of the initial objective reactions ~~are~~ should be treated as equivalent in analyzing the results from clinical trials. Therefore, the Working Group concluded that, in using either the risk assessment-based or safety assessment-based approach to establishing thresholds for major food allergens, those published studies reporting objective reactions should be used and that "determinations … should be based on evidence of the initial objective sign."

These conclusions were evaluated by the FDA Food Advisory Committee (Committee) (July, 2005). In 2005, the Committee stated that "…it is appropriate to conclude that objective responses associated with allergic reactions pose risks to human health." Further, the Committee recognized that information on subjective responses might be applicable in the safety assessment-based approach in that "…when a challenge study recorded the dose at which both subjective and objective responses occurred, that information can be used to select the appropriate uncertainty factor(s)."

Based on our review of the literature as of January 2013, we conclude that the same considerations discussed by the Working Group and the Committee for establishing thresholds also apply to determining which reactions constitute "allergic responses that pose a risk to human health." In other words, an~~y~~ objective reaction in a clinical trial should be considered as indicative of a risk to human health regardless of the specific signs observed, and subjective

symptoms generally should not be considered as indicative of a risk to human health in the absence of objective signs.

Therefore, we consider an~~y~~ objective allergic reaction observed in a clinical trial as an "allergic response that poses a risk to human health" in evaluating the scientific evidence presented in petitions requesting labeling exemptions for specific ingredients. In addition, subjective reactions that are associated with objective reactions at higher doses or that are of sufficient severity to stop a dose escalation study also may be considered allergic responses that pose a risk to human health. If subjective reactions were observed or recorded in a clinical study, we recommend that the petition include a discussion of how those data were used, or why they were not used.

Appendix 2. Animal Testing

Animal models are widely used in toxicology testing to assess the potential effect of a substance in humans. However, as of the date of this guidance document, no appropriate animal model systems have been developed or validated to test potential human allergenicity. Although animals can be induced to become allergic to foods and proteins, there is no animal model that can differentiate between those foods that are commonly allergenic in humans and those that are not, or between allergenic and non-allergenic proteins in an individual food. Further, there are no data indicating that the level of sensitivities in animals reflect those seen in humans, that animals respond in the same manner as humans to modification of allergenic proteins caused by processing, or that animals respond in the same manner as humans to matrix effects. Therefore, we do not recommend the use of animal testing as an independent indicator of either the absence of allergenic protein or of whether an ingredient will cause an allergic response that poses a risk to human health.

In some cases, a submitter may be able to use data from animal testing to supplement the primary data contained in a petition or notification. For example, if the submitter cannot obtain data from a statistically valid number of sensitive individuals in clinical trials or serum studies, the human response data may be supplemented by more extensive animal testing. In that case, we encourage submitters to discuss the design and condition of these tests with us before they make their submission.