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Evaluating the Public Health Importance of Food Allergens Other Than the Major Food Allergens Listed in the Federal Food, Drug, and Cosmetic Act: Guidance for FDA Staff and Interested Parties

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For questions regarding this document, contact the Human Foods Program at HFP-Policy@fda.hhs.gov.

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U.S. Department of Health and Human Services
Food and Drug Administration
Human Foods Program

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Table of Contents

Evaluating the Public Health Importance of Food Allergens Other Than the Major Food Allergens Listed in the Federal Food, Drug, and Cosmetic Act: Guidance for FDA Staff and Interested Parties[1]

This guidance represents the current thinking of the Food and Drug Administration (FDA or we) 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 is intended for:

- FDA staff who are responsible for evaluating, on FDA's initiative or in response to a citizen petition submitted in accordance with 21 CFR 10.30, the public health importance of a non-listed food allergen ("interested FDA staff"), which for the purpose of this guidance means a food allergen other than one of the major food allergens (i.e., milk, eggs, fish, Crustacean shellfish, tree nuts, wheat, peanuts, soybeans, and sesame) listed in the Federal Food, Drug, and Cosmetic Act (FD&C Act); and
- Interested parties who intend to submit a citizen petition asking FDA to establish regulatory requirements based on the public health importance of a non-listed food allergen ("petitioners") or who are interested in how FDA generally intends to evaluate the public health importance of such food allergens.

This guidance addresses substances that are currently consumed in food or have previously been consumed in food, within or outside the United States, such that there is a body of information

[1] This guidance has been prepared by the Division of Chemical Contaminants in the Office of Post-Market Assessment, the Compliance Policy Staff in the Office of Compliance and Enforcement, the Division of Food Labeling and Standards in the Office of Nutrition and Food Labeling, and the Office of Policy, Regulations, and Information, all in the Human Foods Program at the U.S. Food and Drug Administration.

about adverse reactions experienced by consumers who ingest the substance.[2] This guidance does not address the potential that a substance that would be new to the food supply might be a food allergen. This guidance also does not address scientific research regarding potential cross-reactivity to a known food allergen and how this research could help determine whether a substance in food could be a food allergen.[3]

This guidance describes the approach we generally intend to take when we evaluate the public health importance of a non-listed food allergen by specifying:

- The scientific factors that we generally intend to consider when evaluating the public health importance of a non-listed food allergen;
- Other information, relevant to the labeling and production of food containing the food allergen, that we generally intend to consider when evaluating the public health importance of a non-listed food allergen; and
- Our recommendations for how to identify and evaluate the body of evidence applicable to an evaluation of the public health importance of a non-listed food allergen.

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

II. Definitions and Abbreviations Used in This Guidance

A. Definitions of Terms Used in This Guidance

Table 1 defines several terms for the purpose of this guidance.

Table 1. Definitions of some terms used in this guidance

Term	What It Means
Anaphylaxis	An acute, potentially life-threatening allergic reaction with multi-systemic manifestations due to the rapid release of inflammatory mediators
Allergen cross-contact	The unintentional incorporation of a food allergen into a food
Allergenic potency	The amount of allergenic food protein required to elicit a food allergic reaction in an already sensitized individual

[2] The term "food" is defined in section 201(f) of the FD&C Act (21 U.S.C. 321(f)) and means (1) articles used for food or drink for man or other animals, (2) chewing gum, and (3) articles used for components of any such article. Food also includes dietary supplements, as defined in section 201(ff) of the FD&C Act (21 U.S.C. 321(ff)). This guidance pertains to human food.

[3] For information on the topic of clinically cross-reactive food allergy, see section IV.A.

Term	What It Means
Clinically cross-reactive food allergy	Cross-reactivity in which an antibody, usually immunoglobulin E (IgE), directed to one food binds to another food and causes immune-mediated responses (including clinical symptoms) to that other food. (See also the definition of cross-reactivity.)
Community report	A report regarding a known or suspected food allergen in a food product that is submitted to a surveillance database, a research query, or other request for information, or that is otherwise collected and described (e.g., as a patient case study or a diagnostic food challenge study reported in the scientific literature). A community report can be submitted or prepared by consumers, health care professionals, industry, researchers, government agencies, non-government agencies, or other interested parties. Some community reports (e.g., adverse event reports and case studies) describe an allergic reaction experienced by an individual to a food product, whereas other community reports (usually called product complaints) call FDA's attention to a potential problem (e.g., labeling that does not disclose that a food product is or contains a food allergen). See Appendix A for further discussion on community reports.
Cross-reactivity	Reactivity of the immune system observed when a protein in one food shares characteristics with a protein from another substance or food. (See also the definition of clinically cross-reactive food allergy.)
Documented sensitized individual	An individual with documented evidence of sensitization to a relevant food or component(s) of food (e.g., confirmed by positive skin percutaneous test (SPT) or *in vitro* allergen specific test)
Food	The term "food" is defined in section 201(f) of the FD&C Act and means: (1) articles used for food or drink for man or other animals, (2) chewing gum, and (3) articles used for components of any such article (21 U.S.C. 321(f)). Food includes dietary supplements, as defined in section 201(ff) of the FD&C Act (21 U.S.C. 321(ff)). This guidance pertains to human food.
Food allergen	The food or component(s) of a food (often a protein) that elicits specific immunologic reactions (Ref. 1 and Ref. 2)

Term	What It Means
Food allergic reaction	An immune-mediated reaction, characterized by a set of clinical symptoms, experienced by a sensitized or allergic individual exposed to a food allergen
Food allergy	An adverse health effect arising from a specific immune response that occurs reproducibly on exposure to a given food (Ref. 1 and Ref. 2)
Food challenge	A clinical procedure or intervention in which gradually increasing food doses are administered to elicit reactivity to the food. Food challenges can be unblinded (open), single-blinded (in which only the researcher doing the study knows what the participant is receiving), or double-blinded (in which neither the researcher nor the participant know what the participant is receiving).
Food hypersensitivity	An adverse food reaction, occurring in a population of sensitive individuals, that can be either mediated by immune mechanisms (i.e., food allergy) or mediated by mechanisms that are not immune mechanisms (i.e., food intolerance)
Food intolerance	Food adverse reaction that is not immune-mediated (e.g., lactose intolerance)
Frequency dose–response	The population distribution of doses eliciting or provoking a food allergic reaction
Historical information	Generally available information (e.g., in published scientific literature and in community reports)
IgE-mediated food allergy	Food allergy that is mediated by an immune response involving IgE antibody
Interested FDA staff	FDA staff who are responsible for evaluating, on FDA's initiative or in response to a citizen petition submitted in accordance with 21 CFR 10.30, the public health importance of a non-listed food allergen
Major food allergen	Milk, eggs, fish, Crustacean shellfish, tree nuts, wheat, peanuts, soybeans, and sesame and, with few exceptions, a food ingredient that contains protein derived from one of these foods (see section 201(qq) of the FD&C Act)
Objective signs of food allergy	Symptoms that are elicited by food challenge and visible or ascertainable to an observer (e.g., hives, swelling, wheezing)
Oral allergy syndrome	Food allergic condition limited to tingling, itching, or swelling of the lips or mouth after oral contact with a food allergen
Petitioner	An interested party who intends to submit a citizen petition asking us to evaluate the public health importance of a non-listed food allergen

Term	What It Means
Probable food allergy rate	Prevalence estimate of food allergy derived from questionnaires in a population of self-reported allergic individuals
Reactivity (or elicitation)	Development of allergic signs or symptoms when the food or component(s) of food is consumed
Self-reported allergic individual	An individual with self-reported history of food allergic reactions (i.e., typical and reproducible symptoms in close temporal association (e.g., within a few hours) of food consumption) and self-reported doctor-confirmed diagnosis with evidence of sensitization to relevant food or component(s) of food (e.g., positive reaction in SPT or *in vitro* allergen specific test)
Self-reported reactive individual	An individual who self-reports having had a food allergic reaction without also self-reporting evidence of sensitization to relevant food or component(s) of food
Self-reported sensitized individual	An individual who self-reports evidence of sensitization to relevant food or component(s) of food (e.g., a self-report of positive SPT or *in vitro* allergen specific test) without also self-reporting food allergic reaction
Sensitization	Production of antibodies, usually IgE, specific to the food or component(s) of food
Severity dose-response	The gradient of severity of food allergic reactions caused by the food
Subjective symptoms of food allergy	Symptoms that are elicited by food challenge but not visible or ascertainable to an observer (e.g., tingling, chest tightness, nausea)
Threshold (as described in scientific literature)	Level below which it is unlikely that a food allergic individual would experience an adverse effect (Ref. 3). In food challenge studies, the challenge dose interval between the highest challenge dose not to elicit an objective sign or symptom and the lowest challenge dose to elicit an objective sign or symptom (Ref. 4 and Ref. 5).
Well-characterized allergic individual	An individual with documented history of food allergic reactions (i.e., typical and reproducible clinical allergic signs or symptoms in close temporal association (e.g., within a few hours) of food consumption or positive food challenge) and documented evidence of sensitization to relevant food or component(s) of food (e.g., positive reaction in SPT or *in vitro* allergen specific test)

B. Table of Abbreviations Used in This Guidance

See Table 2 for abbreviations used in this guidance.

Table 2. Abbreviations used in this guidance

Abbreviation	What It Means
1999 Codex criteria	Criteria, recommended to Codex by the Food Allergens Labelling Panel, for determining whether there are foods, in addition to the list of foods adopted by Codex in 1999, whose presence should always be declared in the list of ingredients on a food label because of their allergenic properties
Allergen labeling requirements of the FD&C Act	The major food allergen labeling requirements in section 403(w) of the FD&C Act
CAERS	CFSAN Adverse Event Reporting System
CGMP	Current good manufacturing practice
CFSAN	Center for Food Safety and Applied Nutrition
Codex	Codex Alimentarius Commission
DBPCFC	Double-blinded, placebo-controlled food challenge
ED	Eliciting dose
ED01, ED05, ED10, ED50	Eliciting dose required to produce a food allergic reaction in 1%, 5%, 10%, or 50% of the allergic population, respectively
ER	Emergency room
FAO/WHO	Food and Agricultural Organization of the United Nations and World Health Organization
FAO/WHO Expert Committee Report (Part 1)	A 2022 report, issued by the FAO-WHO expert consultation, entitled "Risk Assessment of Food Allergens; Part 1. Review and Validation of Codex Alimentarius Priority Allergen List Through Risk Assessment; Meeting Report"
FDA	U.S. Food and Drug Administration
FD&C Act	Federal Food, Drug, and Cosmetic Act
FALCPA	Food Allergen Labeling and Consumer Protection Act of 2004
FASTER Act	Food Allergy Safety, Treatment, Education, and Research Act of 2021
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
IgE	Immunoglobulin E antibody
ILSI-EU	International Life Sciences Institute-Europe
NASEM	National Academies of Sciences, Engineering, and Medicine
NASEM Report	A 2016 report, issued by NASEM, entitled "Finding a Path to Safety in Food Allergy: Assessment of the Global Burden, Causes, Prevention, Management and Public Policy"
Non-listed food allergen	A food allergen other than one of the major food allergens (i.e., milk, eggs, fish, Crustacean shellfish, tree nuts, wheat, peanuts, soybeans, and sesame) listed in the FD&C Act

Abbreviation	What It Means
OAS	Oral allergy syndrome
OFC	Oral food challenge– open or single-blinded (but not double-blinded)
Part 117	Current Good Manufacturing Practice, Hazard Analysis, and Risk-Based Preventive Controls for Human Food in 21 CFR part 117
Preventive controls requirements	The requirements (primarily in subparts C and G of 21 CFR part 117, with associated requirements in subparts A, D, E, and F of part 117) for domestic and foreign facilities that are required to register under section 415 of the FD&C Act to establish and implement hazard analysis and risk-based preventive controls for human food
SPT	Skin percutaneous test ("skin prick test")

III. Background

A. What Is Food Allergy?

Food allergy is a form of food hypersensitivity. Food allergy can be broadly defined as an adverse health effect arising from a specific immune response that occurs reproducibly on exposure to a given food (Ref. 1 and Ref. 2). A food allergen is the food or component(s) (often a protein) of a food that elicits specific immunologic reactions (Ref. 1).

Adverse reactions to food due to food hypersensitivity can be broadly grouped into reactions that are mediated by either immune mechanisms (food allergic reactions) or non-immune mechanisms (primarily food intolerances) (Ref. 1). For example:

- Adverse reactions that are immune-mediated (food allergic reactions) can be caused by:
  - Immunoglobulin E antibodies (IgE)-mediated mechanisms (e.g., gastrointestinal anaphylaxis);
  - Non-IgE-mediated mechanisms (e.g., celiac disease, food protein-induced enterocolitis);
  - Mixed immune mechanisms (e.g., eosinophilic gastroenteropathies[4]); or
  - Cell-mediated mechanisms (e.g., contact dermatitis).
- Adverse reactions that are not immune-mediated can be caused by:
  - Metabolic mechanisms (e.g., lactose intolerance);
  - Pharmacologic mechanisms (e.g., reaction to caffeine);
  - Toxicological mechanisms (e.g., scombroid toxin poisoning); or
  - Other idiopathic (undefined) mechanisms (e.g., reactions to sulfites).

[4] Although IgE-mediated responses to foods associated with this group of disorders have been identified, the main pathogenesis of this group of disorders is believed to be non-IgE-mediated.

Many different types of food allergies have been identified as causing reactions that adversely impact public health. Food allergies that are mediated by IgE are some of the most well-characterized food allergies. IgE-mediated food allergies are characterized by a period of sensitization in which an individual develops IgE antibodies to a food and then, some time later, becomes reactive upon exposure to that food (Ref. 1 and Ref. 2). More than 160 foods have been shown to cause IgE-mediated food allergic reactions. Such reactions can occur within minutes to hours after a sensitized individual consumes the applicable food allergen and can have a wide range of clinical manifestations (Ref. 1 and Ref. 2). IgE-mediated food allergic reactions can involve a single organ system such as 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). The most severe IgE-mediated food allergic reactions lead to a highly serious health condition called anaphylaxis. Anaphylaxis involves the "shock organs" of the respiratory tract or cardiovascular system and can thus rapidly involve signs or symptoms[5] such as cough, wheezing, swelling of the larynx or vocal cords, and low blood pressure. If untreated, anaphylactic reactions can lead to loss of consciousness, asphyxiation, respiratory failure, shock, or even death (Ref. 1 and Ref. 3). Because of the risk for immediately life-threatening reactions, management of IgE-mediated food anaphylaxis often requires prompt use of medications (e.g., epinephrine autoinjector) and other emergency care measures (e.g., urgent care or emergency room visits, hospitalization) (Ref. 1 and Ref. 2).

Immune-mediated food allergies that are not IgE-mediated (e.g., mechanisms associated with celiac disease) can also present with a constellation of acute or delayed symptoms and with potentially serious adverse health consequences and comorbidities. For example, upon exposure to glutens (i.e., wheat, rye, and barley), symptoms of celiac disease can manifest acutely as severe diarrhea or as more chronic complications such as weight loss, nutrient deficiencies (e.g., anemia, osteomalacia), autoimmune disease, organ damage, and malignancy (Ref. 3). Furthermore, some foods can cause both IgE-mediated and non-IgE-mediated food allergic reactions. For example, while glutens are known to elicit reactions in individuals with celiac disease, they can also trigger IgE-mediated reactions in other types of allergic individuals. Similarly, milk is a well-recognized trigger of IgE-mediated reactions but may also be an important cause of vomiting and diarrhea in individuals with non-IgE-mediated food allergic conditions such as food protein-induced enterocolitis syndrome (FPIES) (Ref. 1). Reactions to foods involving mechanisms that are not immune-mediated (e.g., lactose intolerance) can also involve signs and symptoms of varying severity but are typically not associated with life-threatening health conditions.

The focus of this guidance on evaluating the public health importance of food allergens is IgE-mediated food allergy, which is a type of food allergy that has been studied extensively, is well characterized to cause severe and immediately life-threatening allergic reactions (e.g., anaphylaxis), and causes significant morbidity as well as risk of mortality. Likewise, the discussions in this guidance of "food allergens" focus on those foods that elicit IgE-mediated

[5] See Table 1 for the definitions of "objective signs of food allergy" and "subjective symptoms of food allergy." In the remainder of this guidance, we generally refer to "signs or symptoms" without noting that "signs" are objective and "symptoms" are subjective.

immune reactions.[6] Because some foods can cause both IgE-mediated and non-IgE-mediated reactions, evidence of non-IgE-mediated reactions (e.g., severe diarrhea associated with celiac disease) can be useful as supplemental information in an evaluation of the public health importance of such a food allergen (see discussion in section VI.A.2).

This guidance is informed by FDA's experience with IgE-mediated food allergens. However, as discussed above, we recognize that food allergens acting through other mechanisms may raise public health concerns. FDA intends to evaluate the public health importance of these allergens on a case-by-case basis. We will also continue gathering scientific data and other information on food allergens acting through other mechanisms to help inform possible future action on these allergens, which may include future guidance or communications to the public.

B. Preventing Food Allergic Reactions

Although treatments for IgE-mediated food allergies are currently being developed, the most effective strategy for preventing food allergic reactions is for allergic consumers to avoid foods that are or contain food allergens.[7] Constant food vigilance and fear of accidental life-threatening reactions with every meal are daily, patient-centered challenges that can accompany management of food allergy. These patient-centered challenges have been shown to negatively impact the quality of life of food allergic individuals and their caregivers (Ref. 2).

As discussed in section IV.A, some consumers have clinically cross-reactive food allergies (Ref. 11) in which a consumer who experiences an IgE-mediated allergic reaction to one food allergen (e.g., cashews, which are a tree nut) also experiences IgE-mediated allergic reactions to another food allergen (e.g., pistachios, which also are a tree nut (Ref. 1)). While most individuals with cross-reactive allergies to foods, such as tree nuts, understand the reaction risks for cross-reactivity and are cautioned to avoid all tree nuts to prevent allergic reactions, other cross-reactive food allergies may not be known or obvious to the food allergic consumer. In the latter case, because individuals known to be allergic to a food allergen may have inherent potential for IgE-mediated reactions to other cross-reactive food allergens, first-time and/or any inadvertent consumption of a cross-reactive food allergen by such individuals can also lead to allergic reactions. A particularly challenging situation is one in which a food allergen has not been on the U.S. market for an extended period of time or is not commonly used as an ingredient in food, because potential cross-reactivity to the food allergen would not be well-recognized in the allergic population.[8]

As discussed in section III.C.1, in general the FD&C Act and our implementing regulations broadly apply to the production of food that is or contains a food allergen through statutory and

[6] Adverse reactions that are primarily food intolerances are not immune-mediated and thus not food allergies. Foods or food ingredients primarily causing food intolerances are not considered food allergens and are outside the scope of this guidance.

[7] FDA recently approved the use of oral immunotherapy to treat children and adolescents with peanut allergies (Ref. 8). The oral immunotherapy is indicated for the mitigation of allergic reactions, including anaphylaxis, that can occur with accidental exposure to peanut (Ref. 9 and Ref. 10). Oral immunotherapy currently is available only for peanuts, is used in combination with a peanut avoidance diet, and is not a cure.

[8] For example, see "Consumer Advice on Lupin" (Ref. 12), advising that people who are allergic to peanuts could also react to lupin, a legume belonging to the same plant family as peanuts.

regulatory provisions regarding: (1) food labeling; (2) food production; and (3) the safety of substances added to food. The label of packaged foods provides allergic consumers and their caregivers information they can use to avoid foods that contain food allergens. The most relevant information is the food allergen source from which a food or food ingredient is derived. For example, the source of the food "tofu" is the major food allergen "soy," and the source of the ingredient "lactoferrin" is the major food allergen "milk." The potential for allergen cross-contact can be reduced or eliminated through current good manufacturing practices (CGMPs) and preventive controls. The CGMP requirements and preventive controls requirements apply only to the already identified major food allergens.

Complete avoidance of food allergens remains difficult. This is exemplified by the high percentage (40-50%) of food allergic individuals who report IgE-mediated reactions to major food allergens and other foods in the community every year (Ref. 1, Ref. 13, and Ref. 14). A subset of these food allergic reactions results in anaphylaxis presenting to emergency rooms (Ref. 2). Causes for these reactions are multifactorial – e.g., they can be due to consumption of non-packaged food products in which labeling of the already identified food allergens is not required, allergen cross-contact during food production, or unclear or absent allergen information on packaged food products when a food allergen is not an already identified major food allergen subject to the allergen labeling requirements of the FD&C Act (Ref. 13). For example, a food allergen that is not a major food allergen and is added as a spice, flavoring, or color may be declared using a collective term as allowed for in 21 CFR 101.22. As another example, the food allergen source of a food or ingredient that is not an already identified major food allergen is not required to be disclosed as part of the common or usual name of the food or ingredient.

C. FDA's Regulations, Guidance, Assistance, and Communications Applicable to Food Allergens

1. Regulatory framework applicable to food allergens in the United States

In general, the provisions of the FD&C Act and our implementing regulations that are most relevant to food that is or contains a food allergen address: (1) food labeling; (2) food production (e.g., manufacturing, processing, packing, and holding food); and (3) the safety of substances added to food.

With respect to food labeling, the general misbranding provisions in section 403 of the FD&C Act (21 U.S.C. 343) provide us with broad authority to provide consumers with information on the food label about substances in the food, including substances that are food allergens. We have established several regulations that implement these misbranding provisions of the FD&C Act and also specify some special circumstances that may be relevant to some food allergens. For example, a food label must bear the common or usual name of the food, if it has one, and the common or usual name of each ingredient if the food is made from two or more ingredients (section 403(i) of the FD&C Act). A common or usual name must accurately identify or describe, in as simple and direct terms as possible, the basic nature of the food or its characterizing properties or ingredients and can either be the name established by common use or the name required by a regulation (21 CFR 102.5). For example, the label of a food made with

sugar must declare this ingredient by its common or usual name ("sugar") rather than the chemical name "sucrose" (see 21 CFR 101.4(b)(20); section 403(i) of the FD&C Act). However, specific labeling provisions apply to the declaration of some food ingredients. For example, spices, natural flavor, and artificial flavor may be declared using a collective term (i.e., "spice," "natural flavor," or "artificial flavor," respectively) without identifying the particular spice or flavor, except for substances obtained by cutting, grinding, drying, pulping, or similar processing of tissues derived from fruit, vegetable, meat, fish, or poultry (e.g., powdered or granulated onions, garlic powder, celery powder), which are commonly understood by consumers to be food rather than flavor and must be declared by their common or usual name (see 21 CFR 101.22(h)(1) and (3)).[9] Likewise, some colorings may be declared using the collective term "color" (see 21 CFR 101.22(k)(2)). As another example, incidental additives that are present in a food at insignificant levels and do not have any technical or functional effect in that food are exempt from the ingredient declaration requirements (see 21 CFR 101.100(a)(3)).

In 2004, the Food Allergen Labeling and Consumer Protection Act of 2004 (FALCPA) amended the FD&C Act to provide us with additional, specific authority regarding the labeling of a food (other than a raw agricultural commodity) that bears or contains a "major food allergen."[10] Under section 403(w) of the FD&C Act, a food is misbranded if it contains a major food allergen and fails to declare that major food allergen on its label in the manner specified using the major food allergen's common or usual name, including the name of the food source from which the major food allergen is derived. Section 201(qq)(1) of the FD&C Act (21 U.S.C. 321(qq)(1)) defines a "major food allergen," in part, as any of the following:

- Milk,
- 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,

[9] For the purpose of this guidance:

- We use variations of the term "declare" when that term is used in the FD&C Act, our regulations, or an FDA guidance document to describe information that is present on a food label. For example, the label requirements in 21 CFR 101.4 for the designation of ingredients and our "Guidance for Industry: Questions and Answers Regarding Food Allergens, Including the Food Allergen Labeling and Consumer Protection Act of 2004" (Edition 4)" (Ref. 15) both use variations of the term "declare" when describing information presented on a food label. Likewise, we use variations of the term "undeclared" when describing a label that does not comply with label requirements in the FD&C Act or our food labeling regulations.
- We use variations of the term "disclose" when discussing information that is present on a food label but is not specified in the FD&C Act, our regulations, or an FDA guidance document. For example, we use variations of the term "disclose" to describe voluntary declaration of the food allergen source of a food allergen that is not a major food allergen. Likewise, we use variations of the term "undisclosed" when describing a label that does not provide label information, such as the food allergen source of a food allergen that is not a major food allergen, and when describing a food allergen that our food labeling regulations allow to be declared with a collective term (e.g., "spice," "flavor").

[10] We issued guidance to help the public understand our implementation of the amendments, including what foods and manufacturers are subject to the amendments and labeling requirements (Ref. 15). We also issued guidance to clarify the information we need when considering whether to exempt certain ingredients derived from major food allergens from the allergen labeling requirements (Ref. 16).

- Peanuts, and
- Soybeans.

When FALCPA was enacted, Congress had found that these eight foods and food groups, out of more than 160 identified food allergens, accounted for 90% of food allergic reactions in the U.S. (21 U.S.C. 343 note). When drafting FALCPA, Congress made clear that the new statutory requirements did not alter our existing authority under the FD&C Act to require a label or labeling for other food allergens (21 U.S.C. 343 note). Also, section 403(x) of the FD&C Act gives us explicit authority to require by regulation the disclosure of spices, flavorings, colorings, or incidental additives that are, or contain, food allergens other than the eight major food allergens.[11]

In April 2021, the Food Allergy Safety, Treatment, Education, and Research Act of 2021 (FASTER Act) (Public Law 117-11) amended section 201(qq) of the FD&C Act to add sesame to the definition of "major food allergen." This amendment applies to any food that is introduced or delivered for introduction into interstate commerce on or after January 1, 2023.

With respect to food production, our regulation entitled "Current Good Manufacturing Practice, Hazard Analysis, and Risk-Based Preventive Controls for Human Food" (21 CFR part 117; "part 117") establishes requirements applicable to establishments that manufacture, process, pack, or hold human food. Part 117 includes CGMP requirements to prevent allergen cross-contact. Allergen cross-contact is the unintentional incorporation of a food allergen into a food; part 117 defines "food allergen" to mean a major food allergen as defined in section 201(qq) of the FD&C Act. (See the definitions of "allergen cross-contact" and "food allergen" in 21 CFR 117.3.) Allergen cross-contact occurs between foods that have different food allergen profiles (the food allergen sources present or absent in a food). The processing characteristics of a food can affect the potential for allergen cross-contact to occur. For example, when using shared equipment, it is more difficult to prevent allergen cross-contact when producing foods with high viscosity (e.g., nut butters) and using only dry cleaning methods than when producing foods with low viscosity (e.g., many beverages) and using wet cleaning methods due to challenges associated with cleaning all traces of a high-viscosity food from shared food-contact surfaces using dry cleaning methods. As another example, when using adjacent processing lines, it is more difficult to prevent allergen cross-contact when producing foods (e.g., peanuts and milk powder) that are prone to the creation of dust than when producing foods (e.g., many beverages) that are not prone to the creation of dust.

Part 117 also establishes specific requirements (commonly called "preventive controls requirements") for domestic and foreign facilities that are required to register under section 415 of the FD&C Act to establish and implement hazard analysis and risk-based preventive controls for human food as mandated by the FDA Food Safety Modernization Act of 2011 (FSMA). With few exceptions,[12] these preventive controls requirements specify that food manufacturers

[11] We relied on this authority, in part, to require the labeling of carmine and cochineal extract in foods (see § 73.100 and 74 FR 207, January 5, 2009).

[12] See 21 CFR 117.5 for the exemptions from the preventive controls requirements. For example, the preventive controls requirements do not apply to a facility that is a "qualified facility" (e.g., because it is a very small business)

must implement a food safety plan that includes a hazard analysis to identify known or reasonably foreseeable hazards that require a preventive control. Preventive controls must significantly minimize or prevent hazards. When a hazard requiring a preventive control is a major food allergen, preventive controls also must ensure that the food manufactured, processed, packed, or held by the facility will not be adulterated under section 402 of the FD&C Act (21 U.S.C. 342) or misbranded under section 403(w) of the FD&C Act. (See 21 CFR 117.126, 117.130(a)(1) and (b)(1)(ii), and 117.135(a)(1), (c)(2), and (c)(3).)

With respect to the safety of substances added to food, under sections 201(s) and 409 of the FD&C Act (21 U.S.C. 321(s) and 348), any substance that is intentionally added to food is a food additive that is subject to premarket review and approval by FDA, unless the substance is generally recognized, among qualified experts, as having been adequately shown to be safe under the conditions of its intended use (commonly referred to as a "generally recognized as safe" or "GRAS" substance), or unless the use of the substance is otherwise excepted from the definition of a food additive (e.g., if the substance meets the definition of "color additive" in section 201(t) of the FD&C Act). The procedures for premarket review and approval of a food additive petition are established in 21 CFR part 171. A notification procedure whereby any person may notify FDA of a conclusion that a substance is GRAS under the conditions of its intended use is established in 21 CFR part 170, subpart E.

Under sections 201(t) and 721 of the FD&C Act (21 U.S.C. 321(t) and 379), a substance that meets the definition of "color additive" must be listed in an FDA regulation prescribing the conditions under which such additive may be safely used. In contrast to the definition of food additive, the definition of color additive has no provision for GRAS substances and, thus, all substances that are color additives are subject to premarket review and listing by FDA. The procedures for premarket review of a color additive petition are established in 21 CFR part 71.

When available, information regarding food allergic reactions that are known to occur reproducibly on exposure to a given food substance are relevant to an evaluation of the safety of a substance under the conditions of its intended use. In most circumstances when a substance is subject to premarket review and approval by FDA, the substance is not already in the U.S. food supply and, thus, reactivity information from prior food exposure by the U.S. population would not be available during FDA's premarket review. However, we can and have used our authorities regarding the safety of substances added to food to amend the conditions of use specified in a regulation if information regarding allergic reactions to a food substance becomes available after that food substance has entered the U.S. food supply. For example, in 2009, we relied, in part, on the authority in sections 201(t) and 721 of the FD&C Act to revise our

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as that term is defined in part 117. (Alternative requirements apply to these facilities.) The preventive controls requirements also do not apply with respect to activities that are subject to "hazard analysis and critical control point" requirements in 21 CFR part 120 (for juice) or 21 CFR part 123 (for seafood) if a facility is required to comply with, and is in compliance with, 21 CFR part 120 or 21 CFR part 123, respectively, with respect to such activities. In addition, nonprofit food establishments, restaurants, and retail food establishments are not required to register as a food facility (see 21 CFR 1.226) and generally are inspected by State or local regulatory agencies, often under State or local laws and regulations based on FDA's Food Code, which is a model code available for adoption by local, state, and other jurisdictions to apply to food establishments at the retail level that provide food directly to consumers (Ref. 17).

requirements for cochineal extract and carmine[13] by requiring their declaration by name on the label of all food products[14] that contain these color additives (see § 73.100 and 74 FR 207, January 5, 2009).

2. FDA's Food Code

Food allergen information has been included in FDA's Food Code[15] (Ref. 17) since 2005 and includes a definition of "major food allergen" and a provision under "Demonstration of Knowledge" [Subparagraph 2-102.11(C)(9)] specifying that the person in charge of a food establishment shall have an understanding of the foods identified as major food allergens and the symptoms that a major food allergen could cause in a sensitive individual. The Food Code also allows integration of the allergen labeling requirements of the FD&C Act (see Table 2 for definition) to reflect the additional requirements that apply to food that is packaged at the retail level [Subparagraph 3-602.11(B)(5)]. However, the allergen labeling requirements of the FD&C Act do not apply to foods provided by a retail food establishment that are placed in a wrapper or container in response to a consumer's order – such as the paper or box used to convey a sandwich that has been prepared in response to a consumer's order.

3. FDA's communications to the public

We make safety information available to interested parties on our Web site (https://www.fda.gov). For example, we have issued "Consumer Advice on Lupin" (Ref. 12), advising that people who are allergic to peanuts could also react to lupin, a legume belonging to the same plant family as peanuts.

D. Specific Requests for FDA to Evaluate Certain Foods as Food Allergens of Public Health Importance

Since FALCPA was enacted, we have received several requests to evaluate a food as a food allergen of public health importance. For example:

[13] Cochineal extract is a color additive that is permitted for use in foods and drugs in the United States. The related color additive carmine is permitted for use in foods, drugs, and cosmetics. The Color Additive Amendments of 1960 (Public Law 86–618, 74 Stat. 397) amended the FD&C Act to add the definition of "color additive," establish conditions under which color additives may be safely used, and require FDA to publish a provisional list of color additives that were already in use or were certified as color additives prior to July 12, 1960. FDA included both cochineal extract and carmine in this provisional list. Following FDA's review of color additive petitions submitted in 1964 (for carmine) and 1968 (for cochineal extract), FDA permanently listed both carmine and cochineal extract in the color additive regulations.

[14] The revised requirements also apply to the label of all cosmetic products that contain cochineal extract or carmine.

[15] FDA publishes the Food Code, a model that assists food control jurisdictions at all levels of government by providing them with a scientifically sound technical and legal basis for regulating the retail and food service segment of the industry (e.g., restaurants, grocery stores, institutions such as nursing homes). Local, state, tribal, and federal regulators use the FDA Food Code as a model to develop or update their own food safety rules and to be consistent with national food regulatory policy.

- In 2008, we received a citizen petition asking us to "[amend] ... FALCPA to include barley and rye in the list of common allergens requiring disclosure on packaging" (Ref. 18);
- In 2014, we received a citizen petition asking us to require that sesame seeds and sesame products be regulated in a manner similar to a major allergen under FALCPA and listed specifically by name ("sesame") in ingredient lists of foods, and to add sesame to the list of allergens in the 2005 "Compliance Policy Guide Sec. 555.250 Statement of Policy for Labeling and Preventing Cross-contact of Common Food Allergens" (Ref. 19) to address both labeling and cross-contact issues related to sesame in food manufacturing practices (Ref. 20); and
- In 2015, we received a citizen petition asking us to "issue a regulation to include garlic as an ingredient or allergen on food labels" and specifically "require food labels to list garlic as an allergen" (Ref. 21).

The data and information submitted in support of these requests varied. We denied the request regarding barley and rye because the petition did not include adequate information to show that rye and barley are common causes of severe IgE-mediated food allergies like the major food allergens defined by FALCPA (Ref. 22). We denied the request regarding garlic because: (1) the petition did not provide evidence to show that garlic is a common cause of severe food allergies; and (2) garlic is not considered a spice for purposes of ingredient labeling and must be declared as "garlic" rather than being declared collectively under the term "spice" (21 CFR 101.22(a)(2)). Thus, consumers who are allergic to garlic can avoid consuming it by examining the ingredient statements on the foods they purchase and avoiding those foods where garlic is listed (Ref. 23).

We responded to the request regarding sesame by publishing a notice inviting additional data and other information on the prevalence and severity of sesame allergies in the United States and the prevalence of sesame-containing foods that are sold in the United States but are not required to declare sesame by name as an ingredient (83 FR 54594, October 30, 2018). We stated our interest in learning more about the prevalence and severity of sesame allergies in the United States and the prevalence of sesame-containing foods sold in the United States that are not required to declare sesame as an ingredient. We also stated that we were requesting this data and other information to inform possible regulatory action on sesame to protect and promote the public health. Key scientific data requested for sesame fell into the following two categories:

- Prevalence of allergies and allergic reactions due to sesame in the United States, including the proportion of allergic reactions attributed to undisclosed sesame in food products; and
- Prevalence and amounts of undisclosed sesame in foods.

After considering the data and information submitted to that notice, we announced the availability for public comment of a draft guidance document titled "Voluntary Disclosure of Sesame as an Allergen: Guidance for Industry (Draft Guidance)" (Ref. 24) (85 FR 71920, November 12, 2020). This guidance initiative was intended to provide food manufacturers with FDA's current views on sesame as an allergen and provide recommendations regarding the voluntary disclosure of sesame in certain circumstances where such disclosure was not required,

as well as help individuals who are allergic to sesame identify those foods that contain sesame as an ingredient.[16]

IV. Scientific Factors Relevant to the Public Health Importance of a Non-Listed Food Allergen

We have identified the following scientific factors that we generally intend to consider when evaluating the public health importance of a non-listed food allergen in the United States:

- Factor #1: evidence of IgE-mediated food allergy
- Factor #2: the prevalence of an IgE-mediated food allergy in the U.S. population
- Factor #3: the severity of IgE-mediated food allergic reactions
- Factor #4: the allergenic potency

Our scientific factors are consistent with the 1999 Codex criteria (Ref. 25), the revised criteria recommended by the International Life Sciences Institute-Europe (ILSI-EU) (Ref. 26), published frameworks from ILSI-EU and public, private, and academic partners in Europe for the evaluation of public health importance of a food allergen (Ref. 26 and Ref. 27), publications from ILSI-EU and public, private, and academic partners in Europe that evaluate published frameworks (Ref. 28 and Ref. 29), the National Academy of Sciences, Engineering and Medicine (NASEM) report (Ref. 2; the NASEM report), and the Food and Agricultural Organization of the United Nations and World Health Organization (FAO/WHO) expert consultation on food allergen risk assessment (Ref. 30; the FAO/WHO Expert Committee Report [Part 1]). See Appendix A for further discussion of these criteria and frameworks.

While the discussion from this point forward focuses on IgE-mediated food allergies, as noted previously, we understand that some foods may cause allergic reactions through multiple mechanisms. Therefore, we do not intend to exclude consideration of supplemental data regarding additional immune-mediated mechanisms where relevant in our framework. This is also consistent with the other frameworks discussed further in Appendix A. We will also continue gathering scientific data and other information on food allergens acting through other, non-IgE mechanisms to help inform possible future action on these allergens, which may include future guidance or communications to the public.

A. Evidence of IgE-mediated Food Allergy

An IgE-mediated food allergic reaction is characterized by a two-step immune process – i.e., sensitization and reactivity. Sensitization is the production of IgE specific to the food or food component, often a protein. Reactivity (or elicitation) is the development of clinical allergic signs or symptoms when the food or component of food is consumed. The sensitization and reactivity steps can occur independently in certain individuals, so that evidence of sensitization alone, or reactivity alone, does not establish clear evidence that an adverse reaction to a food is an IgE-mediated food allergic reaction. Therefore, the best approach to a clinical diagnosis of

[16] The FASTER Act amended section 201(qq) of the FD&C Act to add sesame to the definition of "major food allergen," effective January 1, 2023.

IgE-mediated food allergy is robust evidence of a cause-effect relationship between oral exposure to the food or component of food and elicitation of signs or symptoms (which demonstrates reactivity) in individuals who are known to be sensitized to the food (which demonstrates sensitization).

Evidence of IgE-mediated food allergy can be obtained from several sources and methodologies, provided that the sources and methodologies provide evidence of both sensitization and reactivity. The "gold standard" method for obtaining evidence of IgE-mediated food allergy is the double-blinded, placebo-controlled food challenge (DBPCFC) in a population of documented sensitized individuals, because reactivity to food exposure is directly and impartially assessed in documented sensitized individuals. By documented sensitized individuals, we mean individuals with documented evidence of IgE sensitization to the relevant food or component(s) of food (e.g., evidence confirmed by skin percutaneous test (SPT; often called skin prick test) or *in vitro* allergen specific IgE test), but without documented evidence of IgE-mediated food allergic reaction. Conducting the DBPCFC in documented sensitized individuals satisfies the first criterion (sensitization), and elicitation of clinical allergic signs or symptoms during the food challenge provides evidence for the second criterion (reactivity). However, outside of specialized clinical centers, DBPCFC are rarely performed.

When a DBPCFC is not available, other historical information (i.e., from the scientific literature or community reports) can still provide robust evidence of IgE-mediated food allergy, provided that the information provides evidence of both sensitization and reactivity. For example, under appropriate conditions, a positive open or single-blinded oral food challenge (OFC) in a documented sensitized individual can provide robust evidence of IgE-mediated food allergy. Also, evidence of IgE-mediated food allergy can be obtained from historical information describing observations or reports of typical, reproducible, and temporally related signs or symptoms of IgE-mediated food allergic reactions in sensitized individuals, including documented sensitized individuals and self-reported sensitized individuals. Evidence of clinical reactivity in documented sensitized individuals, in whom IgE sensitization has been confirmed, is more robust evidence of IgE-mediated food allergy than evidence in self-reported sensitized individuals, in whom IgE sensitization is not confirmed. Similarly, evidence of positive OFC or other observations of typical, reproducible, and temporally related signs or symptoms associated with food consumption consistent with IgE-mediated allergy is more robust evidence of IgE-mediated food reactivity than reports of unspecified allergic reaction to food alone. Evaluating reactivity information from sensitized individuals in these datasets is important, because it reduces the potential for signs or symptoms reported as food "allergic" reactions to be due to confounders such as an intolerance that might be associated with the food.[17]

Research has identified and characterized specific proteins that have allergenic properties and occur in many different foods. These food allergenic proteins have been recognized by reputable national and international organizations. For example, the World Health Organization and International Union of Immunological Societies (WHO/IUIS) Allergen Nomenclature Sub-committee is an international organization responsible for maintaining and developing a unique, unambiguous, and systematic nomenclature for allergenic proteins and maintains an allergen

[17] For example, the symptoms of lactose intolerance can be a confounder in the diagnosis of milk allergy in individual patients.

database that contains approved and officially recognized allergens (Ref. 31). Identification of a protein from a food in the database maintained by the WHO/IUIS Allergen Nomenclature Sub-committee is supporting evidence that the food or component(s) of food is a food allergen – i.e., that adverse reactions to the food or component(s) of food are IgE-mediated.[18]

Clinical evidence of foods or food components (e.g., proteins) causing IgE-mediated reactions from exposure by non-oral routes (e.g., skin, inhalation) can be used as supporting evidence that an adverse reaction to a food or component of food is IgE-mediated, but generally would not be sufficient, by itself, to be considered definitive evidence that an adverse reaction to a food or component of food is IgE-mediated. The most definitive evidence of IgE-mediated food allergy is from reactions observed or associated with oral or sublingual (i.e., under the tongue) exposure.

Observations in historical information regarding food elimination diets that lead to resolution of chronic signs or symptoms (e.g., eczema, persistent gastrointestinal complaints) in individuals with self-reported sensitization to the food generally do not provide robust evidence of IgE-mediated food allergy unless accompanied by documentation of sensitization and information that typical signs or symptoms are also elicited by food consumption or food challenge in those individuals in a time frame consistent with an IgE-mediated reaction.

In clinically cross-reactive food allergy, IgE directed to a food allergen in one food can bind to, and cause IgE-mediated reactions to, an allergen in another food, likely due to the presence of similar proteins in both foods (Ref. 11). As such, historical information or observed data regarding clinically cross-reactive food allergies (Ref. 11) to a food in individuals sensitized to other cross-reactive foods may provide further evidence of IgE-mediated allergy to that food. For example, a consumer who is known to be allergic to one food allergen (e.g., cashews) could eat a pistachio and experience an immediate allergic reaction. Because both cashews and pistachios are tree nuts and have been recognized to be cross-reactive allergens (Ref. 1), evidence of clinically cross-reactive food allergy to pistachio in a cashew allergic consumer is likely to provide evidence that the individual has IgE-mediated food allergy to pistachio as well. However, while cross-reactive food allergies are important concerns to consider for food allergens, the most definitive evidence that the food causes IgE-mediated food allergy for the purposes of this guidance is evidence that the food directly causes IgE-mediated reactions in individuals who are sensitized to the food.[19]

[18] See the WHO/IUIS submission form for the criteria for submission of a new allergen to the WHO/IUIS allergen nomenclature database (Ref. 31). Section 2.5 of the submission form states: "Allergens are incorporated into the Official List of Allergens only if protein-specific binding of IgE from at least 5 sera of patients allergic to the respective allergen source, and NOT to those without allergy to the source (preference: test with sera from 3 allergic to other sources and 2 without allergies). IgE binding should be tested (demonstrated) to the purified (natural or recombinant) allergen, as well as to an extract of the source material that represents the source of allergy (e.g. fruit, pollen, insect, animal parts)." Section 2.5.1 of the submission form requires evidence of both reactivity and IgE sensitization.

[19] This guidance only addresses food allergy caused by substances that are currently consumed in food or have previously been consumed in food and does not address scientific research regarding potential cross-reactivity to a known food allergen and how this research could help determine whether a substance in food could be a food allergen.

B. Prevalence of IgE-mediated Food Allergy

Information to estimate the prevalence of IgE-mediated food allergy has come from a number of different sources and methodologies, including prospective data from clinic patients who have undergone systematic diagnostic evaluation with clinical testing to the food, self-reported data of food allergy (e.g., responses to questionnaire surveys), review of IgE-mediated food allergic reactions in community reports, and retrospective review of patient medical records with diagnosis codes related to food allergy. Because there are many different types of food hypersensitivities that are not IgE-mediated and other disease processes that may mimic allergic reactions, the most robust estimate of the prevalence rate of an IgE-mediated food allergy is obtained from a defined population of individuals with: (1) documented history of IgE-mediated food allergic reactions (i.e., typical and reproducible signs or symptoms in close temporal association (e.g., within hours) of food consumption or positive food challenge); and (2) documented evidence of IgE sensitization to the relevant food or food proteins (e.g., positive reaction in SPT or *in vitro* allergen specific IgE test) (Ref. 1 and Ref. 2). For the purpose of this guidance, we refer to such individuals as "well-characterized allergic individuals." However, obtaining this type of prevalence rate estimate at the national level is difficult. The 2016 NASEM report (Ref. 2) found that "evidence on the true prevalence of food allergy in the [United States] is obscured by insufficient or inconsistent data and variable methodology." This report did not find prevalence rate estimations for any IgE-mediated food allergy relevant to the U.S. population based on DBPCFC or other robust clinical parameters. Instead, epidemiological studies that estimate "probable food allergy rates" in the general population in the United States are based on self-reported responses to questionnaires distributed to a defined number of participants (commonly called reporters).

In some epidemiological studies to estimate probable food allergy rates, the questionnaires only ask for self-reported information about the foods associated with allergic reactions, whereas in other epidemiological studies to estimate probable food allergy rates, the questionnaires also ask for self-reported information about signs or symptoms, treatment, doctor visits, diagnostic tools, and doctor diagnosis, in addition to self-reported information about the foods associated with allergic reactions. Neither type of epidemiological study can clearly establish that the reporters are well-characterized allergic individuals because the data collected during these studies are self-reported rather than clinically documented. However, the design of the questionnaires used in these studies can increase the probability that the self-reports correctly report food allergy. For example, food allergy rates estimated from epidemiological studies in the general population based only on self-reports of foods associated with an allergic reaction tend to overestimate population prevalence estimates of IgE-mediated allergy to the food (Ref. 1) because many reporters confuse food allergy for other forms of adverse food reactions. This overestimation may be reduced when the questionnaires also ask for self-reported information about signs or symptoms of the allergic reaction(s), treatment or doctor visit, diagnostic tools, and doctor diagnosis, in addition to self-reported information about the foods associated with allergic reactions, because a trained health professional who evaluates the data from the questionnaires could review the additional data to determine whether it is consistent with typical, reproducible, and temporally related signs or symptoms of an allergic reaction and whether there may be evidence of IgE sensitization.

The most robust estimates of probable food allergy rates are obtained from epidemiological studies that: (1) use validated questionnaires and consistent methods to assess the type and characteristics of signs or symptoms experienced during allergic reactions; (2) collect self-reported data from a randomly selected, nationally representative population; (3) ask the reporters to self-report all foods that cause a food allergic reaction (rather than prompt the reporters about only specific foods that cause a food allergic reaction); and (4) ask reporters to describe signs or symptoms, treatment or doctor visits, diagnostic tools, and doctor diagnosis related to food allergy. Asking reporters to identify all foods that cause a food allergy or food allergic reaction can help to provide comparative information on the relative frequency of food allergies to specific food allergens, identify food allergens that have higher or lower prevalence in the population studied, and provide comparative information on the relative number and frequency of IgE-mediated food allergic reactions reported for each food. Asking reporters to also describe the associated adverse effects (signs or symptoms of the allergic reaction(s), treatment or doctor visits, diagnostic tools, and doctor diagnosis) can help strengthen the individual self-reports as likely, or probable, IgE-mediated food allergic reactions.

Another type of epidemiological study that has been used (Ref. 33) to estimate the prevalence rate for a food allergen is an epidemiological study in which researchers look for evidence of IgE sensitization in blood samples collected from the general population. Although this type of study can identify sensitized individuals, it provides no evidence that exposure to the food elicits an allergic reaction in the sensitized individuals and could overestimate the prevalence rate of a food allergen, because some of the sensitized individuals might not be allergic individuals.

Several types of prevalence data generally are not sufficiently robust, by themselves, to estimate prevalence of IgE-mediated food allergy. For example, the following types of prevalence data generally are not robust for the reasons given:

- Prevalence estimates based on IgE sensitization rates or other clinical parameters from local or regional U.S. populations (e.g., academic clinical center patient populations, individuals presenting to local or regional hospital systems) – such data are not nationally representative of the U.S. population.
- Prevalence data from other countries or geographical areas – the U.S. population might have different genetic background, consumption frequencies, or practices for the food(s).
- Information about the frequency of IgE-mediated food allergy and/or IgE-mediated food allergic reactions in community reports from non-questionnaire methods (e.g., surveillance databases) – such reports usually describe a number of allergic individuals without providing sufficient information to understand the baseline number of allergic or non-allergic individuals in the population of reporters.
- Information about the frequency of IgE-mediated food allergy and/or IgE-mediated food allergic reactions from surveys based on retrospective review of patient medical records with diagnosis codes related to food allergy – such diagnosis codes are not always specific for IgE-mediated food allergy.

Prevalence information is more likely to be available for foods that have been on the U.S. market for an extended period of time or are commonly used as an ingredient in food. In addition, the

probable food allergy rate of individual foods generally is not static. Food consumption patterns can change over time – e.g., when newly developed food products that use a food allergen as an ingredient lead to an increased consumption of that food allergen by the U.S population. As a result, information queried over successive time periods could identify changes in probable food allergy rates for individual foods. When multiple reports regarding prevalence data are available, the most recent prevalence reports (e.g., data obtained in the prior 10 years) would more closely reflect the prevalence of allergy to the food in the current population.

In 2004, FALCPA discussed the prevalence of the eight foods that it identified as the major food allergens collectively, stating that these eight foods represented about 90% of all food allergies in the U.S. population and that approximately 2% of adults and about 5% of infants and young children in the United States suffer from food allergies. In 2010, published U.S. food allergy guidelines estimated probable food allergy rates based on self-reported food allergy symptoms to each of these eight major food allergens in the U.S. population to be in the range of 0.3 percent to 3 percent (Ref. 1). Based on more recent 2015-2016 U.S. national surveys (Ref. 34 and Ref. 35), individual probable food allergy rates based on self-reported symptoms highly suggestive of IgE-mediated allergy alone ("convincing" food allergy) for each of these eight major food allergens were estimated to be in the range of 0.6 to 2.9% and 0.5 to 2.2% for adults and children, respectively. Individual probable food allergy rates based on more robust parameters of self-reported "convincing" symptoms and doctor diagnosis ("confirmed" food allergy) for these eight major food allergens in children were estimated to be in the range of 0.2 to 1.8% (Ref. 34). The 2015-2016 U.S. national surveys also reported individual probable food allergy rates for sesame (Ref. 34 and Ref. 35).

See Table 3 for estimated prevalence of IgE-mediated food allergy in the U.S. population for the already identified major food allergens based on probable food allergy rates.

Table 3. Estimated prevalence of probable food allergy to individual already-identified major food allergens in the U.S. population

Population	Milk	Soy	Peanut	Tree Nuts	Fish	Shellfish	Egg	Wheat	Sesame
All ages, self-reported symptoms (% total) (Ref. 1)*	3.0	0-0.6	0.6	0-4.1	0.6	1.2	1.0	0.2-1.3	N/A
Children, ("convincing") symptoms alone (age 0-17; % total) (Ref. 34)	1.9	0.5	2.2	1.2	0.6	1.3	0.9	0.5	0.2

Population	Milk	Soy	Peanut	Tree Nuts	Fish	Shellfish	Egg	Wheat	Sesame
Children, ("confirmed") signs or symptoms and doctor diagnosis (age 0-17; % total) (Ref. 34)	1.0	0.2	1.8	0.9	0.3	0.8	0.7	0.3	0.1
Adults, ("convincing") symptoms alone (age 18+; % total) (Ref. 35)	1.9	0.6	1.8	1.2	0.9	2.9	0.8	0.8	0.2

* The authors reviewed the available data and reported the prevalence of probable food allergy as either a single number or a range based on the findings of their review.

C. Severity of IgE-mediated Food Allergic Reactions

As discussed in section III.A, IgE-mediated food allergic reactions can have a wide range of clinical manifestations that can involve single or multiple organ systems. These clinical manifestations can range from relatively mild local reactions to severe anaphylactic reactions. Without prompt medical intervention with epinephrine or other treatment measures, severe clinical manifestations can progress to various adverse health outcomes, including asphyxiation, respiratory distress, or cardiovascular collapse, often resulting in hospitalization. Severe allergic reactions can be fatal; an analysis of temporal patterns and demographic associations for anaphylaxis in the United States from 1999 to 2010 identified 164 fatalities associated with anaphylactic reactions to food allergens (Ref. 34).

There currently are no validated biomarkers for assessing or predicting reaction severity, and it is likely that several factors (e.g., individual sensitivity, the amount and characteristics of the food consumed, underlying co-morbid conditions such as asthma, the effects of other foods and drugs) all interact to determine the course and severity of each IgE-mediated food allergic reaction (Ref. 1). However, data obtained from clinical studies and from community reports can be used to evaluate the severity of IgE-mediated food allergic reactions at both the individual and population levels. Evidence of the severity of an IgE-mediated food allergic reaction collected from clinical studies, in which a trained health care professional reports or describes, and documents, signs or symptoms generally is more robust than evidence collected from community reports, in which signs or symptoms are self-reported by individuals and may not be objectively scrutinized.

One approach to evaluating severity data obtained from clinical studies or from community reports is the "Grading of Recommendations Assessment, Development and Evaluation" (GRADE) system, which provides a comprehensive and transparent methodology to develop recommendations for the diagnosis, treatment, and management of patients (Ref. 36). A

scientific publication describes a GRADE system for scoring the severity of an IgE-mediated food allergic reaction to an eliciting dose of food (Ref. 37). This GRADE system was developed by integrating eight published schemes or grading systems for the severity of IgE-mediated food allergic reactions, each of which was independently developed and widely recognized (Ref. 37). Another approach to evaluating severity data obtained from information such as DBPCFC studies and from community reports is "PRACTALL" (Ref. 38), which has a numerical grading system for several distinct types of allergic reactions (skin, upper respiratory, lower respiratory, gastrointestinal, and cardiovascular/neurologic).

Factors that are important in characterizing the severity of reaction(s) to the food include the type of elicited signs or symptom(s), the extent of organ involvement, use of certain medications (e.g., epinephrine autoinjector) to manage reactions, evidence of reaction leading to medical visit or hospitalization, or other adverse health consequence. In general, signs or symptoms scored as moderate or severe in this GRADE system pose more risk to the health of allergic individuals than signs or symptoms graded as mild.

See Table 7 in section V.C.4 for an example of a GRADE system for severity data. The GRADE system in Table 7 is adapted from the GRADE systems published in Ref. 37 and Ref. 38.

The most robust evidence of the severity of an IgE-mediated food allergic reaction is collected from a study that reports objective signs in well-characterized allergic individuals evaluated in a clinical setting (e.g., clinic, hospital), that are classified according to a scientifically accepted classification system and treated using an accepted algorithm. In general, the clinical setting of such studies provides a context to assess severity of reaction due to "real-life" allergen exposures in a population of well-characterized allergic individuals presenting to clinical care facilities. This information may also help provide information on the total magnitude of severe reactions in the population to understand the public health burden of allergic reactions to the food.

Documentation of objective signs observed during food challenge studies that are conducted in well-characterized allergic individuals, evaluated as part of a research protocol or clinical evaluation, are also useful. However, these studies may provide less robust evidence of the severity of an IgE-mediated food allergic reaction in allergic individuals than "real-life" allergen exposures because such food challenge studies generally are conducted in a step-wise manner to enhance subject safety. As such, most challenges are conducted with a slow escalation of food allergen exposure and terminated at the first sign of an objective reaction prior to elicitation of severe allergic reactions in most participants (Ref. 1 and Ref. 2). Thus, food challenge studies may not capture the total magnitude of potential severe reactions from exposure to the food allergen.

Evidence of the severity of an IgE-mediated food allergic reaction can be collected from community reports. The quality of the evidence depends on the type of signs or symptoms and the individuals reporting the signs or symptoms. For example, as shown in Table 6 in section V.C.2, the quality of the evidence is greater when:

- The community reports are from well-characterized allergic individuals;

- The reported reactions are objective (i.e., signs such as hives, swelling, and wheezing that are visible to an observer) rather than subjective (i.e., symptoms such as tingling and chest tightness that are not visible to an observer); and
- The reported signs or symptoms are typical of allergic reactions.

In 2004, FALCPA discussed the severity of eight major food allergens collectively, stating that roughly 30,000 individuals require emergency room treatment each year and 150 individuals die each year because of allergic reactions to food. To assess more current markers of severity for major food allergens, we reviewed published scientific literature that identified some objective measures on number or frequency of severe IgE-mediated food allergic reactions reported in U.S. children or adults with probable food allergy to individual, already identified major food allergens, including sesame (Ref. 34 and Ref. 35). See Table 4 for the severity information that we extracted from this published scientific literature.

Table 4. Objective measures of severity of IgE-mediated food allergic reactions in U.S. children (ages 0-17) or adults (age 18+) with probable food allergy to individual, already identified major food allergens

Children or adults with probable food allergy	Milk	Soy	Peanut	Tree Nuts	Fish	Shellfish	Egg	Wheat	Sesame
% of children reported to have severe food allergy (Ref. 34)	25.3	36.8	59.2	56.1	49.0	48.7	28.1	36.7	27.2
% of children reported to have ER* visits- lifetime (Ref. 34)	47.1	53.5	50.4	49.4	69.8	54.9	56.4	43.7	58.2
% of adults reporting severe reactions (Ref. 35)	39.3	45.4	67.8	61.3	56.5	56.8	39.4	42.6	39.7
% of adults reporting ER visits- lifetime (Ref. 35)	47.0	48.3	62.3	54.3	60.1	45.3	55.0	43.6	66.2

* ER = emergency room

D. Allergenic Potency

All food allergens that cause IgE-mediated food allergy have the potential to cause anaphylaxis or other severe health consequences if the food allergen is consumed (Ref. 1 and Ref. 2).

Allergenic potency is the amount of food allergenic protein required to elicit an Ig-E mediated food allergic reaction in a sensitized individual (Ref. 26).

Allergenic potency can vary between individuals and foods. An example of a measure of allergenic potency of a food allergen is the lowest amount (or threshold) of a food allergen required to cause an IgE-mediated food allergic reaction. This can be measured at an individual or population level.[20] Evidence regarding the potency of a food allergen can be collected from studies conducted in a large number of allergic individuals; it also can be collected from case or community reports. As with evidence regarding the severity of an IgE-mediated food allergic reaction, evidence regarding the potency of a food allergen generally is more robust when it is collected from studies, in which a trained health care professional reports or describes, and documents, information (rather than from community reports, in which information is self-reported).

One useful endpoint for assessing the allergenic potency of an individual food is the "frequency dose-response" – i.e., the population distribution of doses eliciting or provoking an IgE-mediated food allergic reaction (Ref. 26). The most robust measure to determine frequency dose-response is data collected from scored food challenge studies conducted over a wide range of doses in a large number of well-characterized allergic individuals.[21] In such studies, the amount of food allergen (in grams of protein) is measured prior to consumption and given in escalating doses until a food allergic reaction is observed.[22,23] The challenge dose associated with the observed reaction is called the eliciting dose (ED) and this dose represents the relative potency of the food allergen for that given individual. Distributions of individual ED information can be modeled to generate probabilities of reactions at a given ED within the population of challenge subjects. For example, international efforts, by organizations such as the Allergen Bureau of Australia & New Zealand, have applied quantitative risk modeling approaches to studies of threshold[24] EDs to food(s) from different food challenge study datasets to determine population ED distributions for different food(s) (Ref. 39 and Ref. 40). From ED distributions, probabilistic information on what EDs could cause a reaction in a given percentage of food allergic individuals within the population can be estimated. For example, dose potencies can be estimated from EDs predicted to produce an IgE-mediated food allergic reaction in 1 percent, 5 percent, or 10 percent of the allergic population (referred to as the ED01, ED05, or ED10, respectively). Also, a measure of mean dose potency could then be the ED predicted to produce an IgE-mediated food allergic

[20] This threshold measure of allergenic potency can help provide information about the potential for any incidental exposure to food to cause an allergic reaction in an individual or in a population of individuals (Ref. 26 and Ref. 27).
[21] The ED information obtained from these studies is similar to the lowest observed adverse effect level (LOAEL) obtained from toxicological studies (Ref. 3).
[22] The DBPCFC is considered to be the best format for an oral challenge, but single-blinded or open challenges could also be appropriate depending on the nature of the product and the food allergic population (e.g., infants).
[23] See "Guidance for Industry: Food Allergen Labeling Exemption Petitions and Notifications" (Ref. 16) for details regarding our recommendations for relevant clinical information to be assessed from challenge study data. The recommended clinical information includes specifying the number of individuals enrolled and challenged in each study, obtaining clinical information for each individual challenged (such as age, gender, nationality/race, SPT or food-specific IgE levels, history of food allergic disease (e.g., frequency, severity of prior reactions), co-morbidities, and assessing information on elicited symptoms to understand potential dose-response severity.
[24] The threshold ED in this case is the challenge dose interval between the highest challenge dose not to elicit an objective reaction/symptom, i.e., no observed adverse effect level (NOAEL), and the ED or LOAEL, i.e., lowest challenge dose to elicit an objective reaction (Ref. 4 and Ref. 5).

reaction in 50 percent of a specific allergic population (referred to as the ED50). This mean potency provides a robust statistical estimate to compare potencies between different food allergens (Ref. 27). Population threshold response distributions were assessed in the FAO/WHO Expert Committee Report (Part 1) to determine potency comparisons between different priority allergens (Ref. 30).

Another endpoint for assessing allergenic potency is the "severity dose–response" – i.e., the gradient of severity of IgE-mediated food allergic reactions caused by the food. The probability of a severe IgE-mediated food allergic reaction from a relatively small amount of a food allergen is greater when the severity dose-response ratio is high (i.e., the food allergen has a high probability of severe IgE-mediated food allergic reactions from low dose exposures)[25] (Ref. 26).

Currently, at the individual level, the most robust measure of allergenic potency is ED information obtained from a scored food challenge study. However, individual allergenic dose potency information can also be obtained through evaluation of case or community reports when the allergen dose exposure can be estimated from quantitative information about both the amount of food product likely consumed during a reaction and the concentration[26] of food allergen in that food product. Quantitative information about both the amount of food product consumed (e.g., in grams or ounces of food product) and the concentration of food allergen in that food product (e.g., parts per million (ppm)) can distinguish between circumstances in which an IgE-mediated food allergic reaction associated with a relatively small amount of food product is due to high allergenic dose potency (when the concentration of food allergen in that small amount of food product is relatively low) or is due to a high concentration of the food allergen in that food product. In contrast, qualitative information about the amount of food product consumed (e.g., a single bite) without any quantitative information about the concentration of food allergen in that food product provides less robust information on allergenic dose potency, because it cannot distinguish between circumstances in which an IgE-mediated food allergic reaction associated with a relatively small amount of food product is due to high allergenic dose potency or is due to a high concentration of the food allergen in that food product.

Data from animal or *in vitro*/*ex vivo* models of IgE-mediated food allergy can provide information relevant to determining allergenic potency, but generally are considered supporting data that are used in combination with – not instead of – human data.

See Table 5 for allergenic potency information for the already identified major food allergens based on more recent published scientific literature (Ref. 8, Ref. 30, and Ref. 41).

[25] Obtaining reliable severity dose-response data from food challenges may be difficult because food challenges are often terminated before severe or anaphylactic responses are elicited.

[26] The concentration could be obtained from the manufacturer of the food product or determined by analysis. When the concentration is known, the allergen dose exposure can be calculated by multiplying the amount of food product reported to be consumed by the concentration of allergen in that food product.

Table 5. Potency reported in the scientific literature for the already identified major food allergens

Measure of Potency	Milk	Soy	Peanut	Tree Nuts	Fish	Shellfish	Egg	Wheat	Sesame
ED01 (mg protein)* (Ref. 8)	0.3	0.7	0.7	0.2-0.04	1.3	30.8	0.2	1.1	0.2
ED05 (mg protein)** (Ref. 8)	3.1	14.1	3.9	0.09-4.7	15.6	429	2.4	9.3	4.2
ED10 (mg protein)*** (Ref. 30)	9.6	61.6	9	5.6-19.3	45.6	1265	7.4	23.9	16.1
ED50 (mg protein)**** (Ref. 41)	192	2858	236	360-728	793	18867	134	279	443

* ED01 represents the cumulative eliciting dose predicted to produce an IgE-mediated food allergic reaction in 1 percent of a specific allergic population.
** ED05 represents the cumulative eliciting dose predicted to produce an IgE-mediated food allergic reaction in 5 percent of a specific allergic population.
*** ED10 represents the cumulative eliciting dose predicted to produce an IgE-mediated food allergic reaction in 10 percent of a specific allergic population.
**** ED50 represents the cumulative eliciting dose predicted to produce an IgE-mediated food allergic reaction in 50 percent of a specific allergic population.

V. Identifying and Systematically Evaluating the Body of Evidence Applicable to Our Scientific Factors

In this guidance, we focus on the identification and evaluation of "historical information" – i.e., generally available information (e.g., in published scientific literature, in community reports), because in most circumstances we expect that such historical information will be the principal information that interested FDA staff or petitioners will consider when evaluating whether a food allergen is of public health importance. (See the definition of "historical information" in Table 1.) However, we do not intend this focus on historical information to preclude interested FDA staff or petitioners from conducting new studies or otherwise obtaining information that does not satisfy the definition of "historical information."

A. Preliminary Identification of Published Scientific Literature

We recommend that petitioners and interested FDA staff conduct a preliminary identification of published scientific literature applicable to our scientific factors through a systematic identification of published abstracts of available English language scientific literature. Applicable scientific literature includes published studies (e.g., clinical, animal, *in vitro*, *ex vivo*

studies) as well as publicly available scientific information provided by reputable national and international organizations.[27]

Examples of key words to use during searches are allergy, IgE and IgE-mediated, natural history, prevention, treatment/desensitization, prevalence, potency, threshold/eliciting dose, dose response, anaphylaxis, severity, cross-reactivity, adverse reactions or events, food analytical surveys, consumer studies, and quality of life.

B. Preliminary Identification of Community Reports in Surveillance Databases and Other Sources

We recommend that petitioners and interested FDA staff conduct a preliminary identification of community reports that are not in the published scientific literature by conducting a systematic review of:

- Publicly available surveillance databases[28] (e.g., the CFSAN Adverse Event Reporting System (CAERS)) for:
  - Adverse event reports regarding food products that disclose the presence of the food allergen; and
  - Product complaints about food products that do not disclose the presence of the food allergen; and
- Other sources describing community reports, such as an FDA request for data and other information and information submitted to the docket established at https://www.regulations.gov for such a request.

C. Systematic Evaluation of Published Scientific Literature and Community Reports

1. Narrowing the identified body of published scientific literature

We recommend that petitioners and interested FDA staff narrow the identified body of published scientific literature to those most likely to be relevant to our scientific factors before conducting a substantive review of the full text of the identified publications. One example of an approach to doing so is to systematically review and classify the scientific abstracts identified during the published scientific literature review as to their likely significance – e.g., as "critical," "supplemental," or "neither critical nor supplemental" as follows:

- Examples of Scientific Abstracts That Could Be Classified as Critical
  - IgE-mediated reactions to food;
  - Exposure: oral, sublingual;

[27] An example of such an organization is the WHO/IUIS Allergen Nomenclature Sub-committee (Ref. 31).
[28] Interested FDA staff also could access information in FDA databases that are not publicly available. For example, if FDA found consumer complaints in a non-public FDA database, we could consider that information and, as appropriate, place redacted information into the administrative record. Examples of relevant information sources are ORADDS (Office of Regulatory Affairs Reporting, Analysis, and Decision Support System) and RES (FDA Recall Enterprise System).

  - Study identifies and characterizes food allergenic proteins and/or food allergic individuals;
  - Original research or systematic reviews, controlled trials, experimental studies, descriptive studies (comparative, correlation, or case-controlled studies), expert committee reports, or opinions or clinical experience of respected authorities, laboratory-based studies, case reports; and
  - Study purpose relevant to incidence/prevalence/natural history; food challenge-diagnosis, threshold; treatment/management/prevention of food-induced anaphylaxis and other acute IgE-mediated food allergic reactions; analytical product surveys and/or label reviews; consumer avoidance practice surveys; quality of life
- Examples of Scientific Abstracts That Could Be Classified as Supplemental
  - Non IgE-mediated reactions to the food;[29]
  - *In vitro* or *ex vivo* studies of dose response to food;
  - Non-oral route of exposure: skin, inhalation, or other non-oral route; and
- Neither Critical Nor Supplemental – articles that cannot be classified as either critical or supplemental.

Following such a classification, a more thorough review could focus on those scientific publications classified as "critical," extend to review of scientific publications classified as "supplemental" as necessary and appropriate (e.g., if there are insufficient data and information available in scientific publications classified as "critical"), and exclude scientific publications classified as "neither critical nor supplemental."

Another example of an approach to narrowing the identified body of published scientific literature to those most likely to be relevant to our scientific factors is to focus the substantive review on those scientific publications that could be scored "High" using a GRADE system (such as that shown in Table 6 in section V.C.2) if such publications applicable to our scientific factors are available.

2. Systematic evaluation of the strength of the identified evidence

We recommend that petitioners and interested FDA staff score each piece of the identified body of evidence based on a strength of evidence GRADE system. See Table 6 for an example of such a GRADE system. We developed and modified the GRADE system in Table 6 from the published scientific literature (Ref. 28 and Ref. 29). We generally intend to use the GRADE system shown in Table 6 when we evaluate the strength of the identified scientific evidence.

[29] Non-IgE-mediated reactions to food allergens may be captured in probable food allergy rates and other community report data.

Table 6. GRADE system for scoring the strength of the evidence applicable to each scientific factor (developed and modified from Ref. 28 and Ref. 29)

If the factor is …	And the type of scientific evidence is …	Then the strength of the evidence is …
Evidence of IgE-mediated food allergy	Historical information of positive DBPCFC in a population of documented sensitized individuals	High (gold standard)
Evidence of IgE-mediated food allergy	Independent recognition of well-characterized proteins from the food as clinically relevant food allergens by reputable national and international organizations	High
Evidence of IgE-mediated food allergy	Historical information of typical, reproducible, and temporally related signs or symptoms of IgE-mediated food allergic reactions in documented sensitized individuals	High
Evidence of IgE-mediated food allergy	Historical information of typical, reproducible, and temporally related signs or symptoms of food allergic reactions in self-reported sensitized individuals	Medium
Evidence of IgE-mediated food allergy	Historical information of typical, reproducible, and temporally-related signs or symptoms of IgE-mediated food allergic reactions in individuals who are not sensitized and/or whose sensitization status is not reported	Low
Evidence of IgE-mediated food allergy	Historical information in documented or self-reported sensitized individuals who do not present typical, reproducible, and temporally related signs or symptoms of IgE-mediated food allergic reactions	Low
Evidence of IgE-mediated food allergy	Elimination diets leading to resolution of chronic signs or symptoms (e.g., eczema, gastrointestinal disturbances) in documented or self-reported sensitized individuals who do not present typical, reproducible, and temporally related signs or symptoms of IgE-mediated food allergic reactions	Low
Evidence of IgE-mediated food allergy	Historical information regarding clinically cross-reactive food allergies to the food in individuals sensitized to other cross-reactive foods	Low
Prevalence	Epidemiological studies in U.S. general population of prevalence rate estimates in well-characterized allergic individuals	High

If the factor is …	And the type of scientific evidence is …	Then the strength of the evidence is …
Prevalence	Epidemiological studies in the U.S. general population to determine probable food allergy rate in self-reported allergic individuals based on the responses to questionnaires that ask about foods that elicit an allergic reaction, signs or symptoms of the allergic reaction(s), treatment or doctor visit, diagnostic tools, and doctor diagnosis	High to medium
Prevalence	Epidemiological studies in the U.S. general population to determine probable food allergy rate in self-reported reactive individuals based on the responses to questionnaires that only ask about foods that elicit an allergic reaction (without also asking for information on signs or symptoms, treatment or doctor visit, diagnostic tools, and doctor diagnosis)	Medium
Prevalence	Epidemiological studies that look for evidence of IgE sensitization in the U.S. general population	Medium
Prevalence	Prevalence data based on sensitization rates or other clinical parameters from populations outside the United States	Medium to low
Prevalence	Prevalence data based on sensitization rates or other clinical parameters from local or regional U.S. populations (e.g., academic clinical center patient populations, individuals presenting to local or regional hospital systems)	Low
Prevalence	Surveys based on retrospective review of patient medical records with diagnosis codes related to food allergy	Low
Prevalence	Surveys based on review of frequency of food allergic reactions in community reports from surveillance databases	Low
Severity	Objective signs, in well-characterized allergic individuals evaluated in a clinical setting (e.g., clinic, hospital), classified according to scientifically accepted classification system, and treated	High
Severity	Documented report of fatality associated with exposure to a food allergen	High

If the factor is …	And the type of scientific evidence is …	Then the strength of the evidence is …
Severity	Objective signs, in well-characterized allergic individuals, elicited by food challenge study	Medium
Severity	Objective signs, typical of allergic reactions, reported in community reports from self-reported or well-characterized allergic individuals	Medium
Severity	Atypical and/or poorly described objective signs reported in community reports by self-reported or well-characterized allergic individuals	Low
Severity	Subjective symptoms elicited by food challenge study in self-reported or well-characterized allergic individuals	Low
Potency	Scored food challenge studies with a wide range of doses to determine threshold EDs in adequate numbers of randomly selected well-characterized allergic individuals	High
Potency	Quantitative risk modeling of threshold EDs to food(s) from different challenge datasets to determine the distribution of EDs to food(s) in a population(s) of well-characterized allergic individuals	High
Potency	Case or community reports describing reactions to quantitatively estimated doses (amounts) of allergen in self-reported or well-characterized allergic individuals	Medium
Potency	Case or community reports describing reactions to qualitatively estimated doses (amounts) of allergen in self-reported or well-characterized allergic individuals	Low

3. Systematic evaluation of community reports

We recommend that petitioners and interested FDA staff group the information based on the type of community report (e.g., individual patient case study, diagnostic food allergy study, adverse event report, product complaint) before systematically evaluating the information in each community report, because the information in a community report, and the quality of such information, can vary depending on the type of community report. For example, solicited information obtained from a standardized questionnaire, information collected by objective observations, and information obtained by systematic review of reactions or reaction history by trained health care professionals are more likely to provide sufficient details to be analyzed compared to unsolicited information or information that is solicited without using a standardized questionnaire.

As applicable to the type of community report and the information it contains, we recommend that petitioners and interested FDA staff identify the following information in each report to aid in systematically evaluating the information:

- Type of report (e.g., individual patient case study, diagnostic food allergy study, adverse event report, product complaint);
- Detailed information about the reporter's food allergies (e.g., type and number of food allergies, how diagnosed, whether there is documented evidence of food-specific IgE sensitization and documented history of IgE-mediated food allergic reactions);
- Consumer demographics and other pertinent clinical history (e.g., allergic conditions, such as eczema, asthma, allergic rhinitis, chronic urticaria, drug allergy or nonallergic medical conditions and medication use); name and type of product and whether the food allergen and its food allergen source were disclosed;
- Detailed signs or symptoms (with emphasis on the severity of reaction);
- Adverse health consequences (e.g., medication use or medical visit (including hospitalization));
- Estimated amount of food product consumed;
- Estimated concentration or amount (ideally in grams of food protein) of food allergen in food product consumed;
- Photos of, or other evidence pertaining to, product labels or complaint information; and
- Other relevant information from the report narrative.

When systematically evaluating community reports classified as adverse event reports or product complaints, it may also be helpful to have information relevant to the labeling and production of food containing the food allergen to better understand the circumstances in which allergic reactions to the food are occurring. Thus, we recommend that petitioners and interested FDA staff also identify the following information:

- Number of adverse event reports and product complaints regarding a food allergen that is:
  - **Disclosed** on the label of food products; and
  - **Not disclosed** on the label of food products;
- Frequency of severe adverse reactions reported to the food allergen that is:
  - **Disclosed** on the label of food products; and
  - **Not disclosed** on the label of food products;
- Type or form of product identified in the complaint – e.g.:
  - Packaged food; or
  - Unpackaged food sold at retail (e.g., food served in a restaurant);
- The potential or suspected cause of an adverse event report or product complaint – e.g.:
  - The label is incomplete or incorrect;
  - The food allergen source of a declared ingredient is not identified;
  - A spice, flavor, or color is declared using a collective term (e.g., "spice," "natural flavor," "artificial flavor," "color") in the ingredient list;

- The food allergen source is a clinically cross-reactive allergen (e.g., if a consumer who is allergic to peanuts eats a product containing lupin); or
- A food allergen appears to have been unintentionally incorporated into a food during its manufacture (e.g., because a consumer who is allergic to a particular food allergen reports a food allergic reaction to a product that does not contain that particular food allergen as an ingredient).

4. Systematic evaluation of the severity of an IgE-mediated food allergic reaction

We recommend that petitioners and interested FDA staff evaluate the severity of an IgE-mediated food allergic reaction described in the identified scientific evidence using a GRADE system. See Table 7 for an example of such a GRADE system.[30] The GRADE system in Table 7 is adapted from the GRADE system published in Ref. 37, with some modifications to signs or symptoms that could be classified as mild, moderate, or severe based on other GRADE systems (Ref. 38) and to classify the severity of an IgE-mediated food allergic reaction based on actual adverse health consequences or interventions (e.g., medication use, hospitalization) that may be found in adverse event data or reports.

In evaluating severity of IgE-mediated food allergic reactions, we recommend that petitioners and interested FDA staff also consider available patient-centered information such as data from quality-of-life studies or questionnaires. Although not part of the systematic grading of severity of an IgE-mediated food allergic reaction, such information addresses other health factors or potential comorbidities associated with allergy to the food such as patients' experiences and perspectives about IgE-mediated food allergic reactions and allergen avoidance practices that may negatively impact the quality of life and psychosocial wellbeing of these individuals and their caregivers (Ref. 2).

Table 7. GRADE system for scoring severity of an IgE-mediated food allergic reaction (adapted from Ref. 36 and Ref. 37)

GRADE	Objective signs or subjective symptoms within a single organ system	Objective signs or subjective symptoms within multiple organ systems
Mild	Skin (not generalized): eczema, erythema, flushing, pruritis, urticaria (hives), conjunctivitis, nonlaryngeal angioedema (e.g., lip swelling) Gastrointestinal (GI): OAS (oral allergy syndrome), nausea alone, colic Upper respiratory: rhinitis, nasal congestion, sneezing	Not applicable; when signs or symptoms appear in multiple organ systems, the signs or symptoms are considered either moderate or severe

[30] We generally intend to use the GRADE system shown in Table 7 when we evaluate the severity of an IgE-mediated food allergic reaction described in the identified scientific evidence.

GRADE	Objective signs or subjective symptoms within a single organ system	Objective signs or subjective symptoms within multiple organ systems
Moderate	Skin: generalized urticaria (hives), facial swelling GI: abdominal pain, diarrhea, vomiting, cramps Upper or mild lower respiratory: dyspnea, cough, chest or throat tightness Cardiovascular/neurologic (mild): tachycardia, dizziness, near syncope, tiredness/lethargy Reaction requiring emergency medical visit (no epinephrine) or loss of school/work activity	Combination of signs or symptoms in any two of the following organ systems of mild/moderate score: Skin; GI; Upper respiratory; Mild lower respiratory; or Cardiovascular/neurologic
Severe	Lower respiratory: asthma, bronchoconstriction (drop in peak flow), wheezing, stridor, hoarseness, laryngeal edema (or throat closing) Cardiovascular/neurologic: arrhythmia, shock, fall in blood pressure, hypotension, cyanosis Anaphylaxis, collapse Reaction requiring epinephrine treatment Reaction requiring hospitalization Death	Any combination of severe signs or symptoms; or Any combination of signs or symptoms in three or more organ systems of mild/moderate score

VI. FDA's Evaluation of the Public Health Importance of a Non-Listed Food Allergen

In this section, we describe FDA's evaluation of the identified body of evidence applicable to our scientific factors, FDA's evaluation of information relevant to the labeling and production of food containing a food allergen, and how we intend to consider the total body of evidence.

A. FDA's Evaluation of the Identified Body of Evidence Applicable to Our Scientific Factors

Sections VI.A.1 through VI.A.4 describe how we generally intend to weigh the evidence for each scientific factor. We generally intend this evaluation to be a case-by-case approach (Ref. 27) based on a robust identified body of evidence – i.e., an identified body of evidence that receives a score of High or Medium using the GRADE system described in Table 6. Therefore, it is unlikely that we would consider that a food or a component of food is a food allergen of public health importance if most or all of the available data and information have a score of Low.

1. Factor #1: Evidence of IgE-mediated food allergy

As discussed in section III.A, this document addresses the food allergies that have been most studied and understood clinically – i.e., IgE-mediated food allergies. Therefore, the initial question for us to address when we evaluate the public health importance of a food or component of food as a food allergen is whether there is robust evidence that an adverse reaction to the food or component of food is IgE-mediated (Factor #1). We generally expect to score data addressing

this initial question as "High" or "Medium" if the data provides evidence of a two-step immune process – i.e., both sensitization and reactivity. We generally do not expect to continue to evaluate the identified body of evidence applicable to Factors #2, #3, and #4 if the identified body of evidence applicable to Factor #1 does not provide robust evidence that an adverse reaction to a food or component of food is, in whole or in part, IgE-mediated.

As discussed in section IV.A, the "gold standard" method for obtaining evidence demonstrating that an adverse reaction to a food or component of food is IgE-mediated is DBPCFC in a population of documented sensitized individuals. We recommend that any request for us to evaluate a food or component of food as a food allergen of public health importance include data from a DBPCFC in a population of documented sensitized individuals whenever possible. We generally intend to score such data as "High" (see Table 6). We recommend that petitioners and interested FDA staff determine whether one or more proteins that are present in a food have been included in a consensus database of well-characterized allergenic proteins, such as the one maintained by the WHO/IUIS Allergen Nomenclature Sub-committee (Ref. 31). We generally intend to consider evidence obtained from DBPCFC in a population of documented sensitized individuals and evidence of one or more well-characterized allergenic proteins from a food, alone or in combination, as the most robust evidence supporting the initial question of whether an adverse reaction to a food or component of food is IgE-mediated.

If data from a DBPCFC in a population of documented sensitized individuals are not available, we generally intend to evaluate, on a case-by-case basis, whether other data and information that can be scored as "High" or "Medium," alone or in combination, provide robust evidence that an adverse reaction to a food or component of food is IgE-mediated. For example:

- We generally intend to score as "High" historical information of typical, reproducible, and temporally related signs or symptoms of IgE-mediated food allergic reactions in documented sensitized individuals (see Table 6). Data obtained from documented sensitized individuals can reduce the potential for reported signs or symptoms of IgE-mediated food allergic reactions to be due to confounders such as an intolerance that might be associated with the food.
- We generally intend to score as "Medium" historical information of typical, reproducible, and temporally related signs or symptoms of IgE-mediated food allergic reactions in self-reported sensitized individuals. Because IgE sensitization to the food is self-reported but not confirmed, data obtained from self-reported sensitized individuals can be confounded by factors such as an intolerance that might be associated with the food.

We generally intend to score as "Low" historical information that fails to provide evidence of a two-step immune process – i.e., both sensitization and reactivity (see Table 6).

2. Factor #2: Prevalence of an IgE-mediated food allergy in the U.S. population

We recommend that any request for us to evaluate a food or component of food as a food allergen of public health importance include prevalence data with a score of "High" or

"Medium" as shown in Table 6. However, we recognize that there could be circumstances in which we will need to evaluate the public health importance of a food allergen with minimal prevalence information – e.g., if a food allergen that causes IgE-mediated reactions is newly introduced to the U.S. food supply and there has not been enough time to design and execute prevalence studies.

As discussed in section IV.B, prevalence rate estimations for any IgE-mediated food allergy based on DBPCFC or other robust clinical parameters are difficult to obtain at the national level, and the NASEM report (Ref. 2) did not find U.S. prevalence rate estimations for any IgE-mediated food allergy based on this type of information. Therefore, we generally expect prevalence data to be based on epidemiological studies to determine probable food allergy rates using self-reported data from questionnaires (see Table 6).

When evaluating epidemiological studies to estimate probable food allergy rates based on self-reported responses to questionnaires, the quality of evidence and information solicited, collected, and analyzed can vary widely. Thus, we generally intend to give greatest weight and score ("High") to studies using questionnaires that:

- Solicit and analyze information such as signs or symptoms, treatment or doctor visits, diagnostic tools, and doctor diagnosis in addition to self-report of food allergy;
- Are directed to a random, nationally representative population in the United States rather than to a targeted population (e.g., to persons identified by physicians as potentially allergic to a specific food allergen);
- Ask reporters about all foods that cause a food allergic reaction (rather than prompt reporters about specific foods that cause a food allergic reaction); and
- Are relatively recent (e.g., data obtained in the prior 10 years).

We generally intend to score as "Medium" epidemiological studies to estimate probable food allergy rates in reactive individuals based on the responses to questionnaires that only ask about foods that elicit an allergic reaction (without also asking for any information on signs or symptoms, treatment or doctor visit, diagnostic tools, and doctor diagnosis) or the responses to questionnaires that solicit incomplete information on signs or symptoms, treatment or doctor visits, diagnostic tools, doctor diagnosis, and/or other methodologies to more effectively characterize self-reported allergic individuals.

We generally intend to score as "Medium" an epidemiological study in which researchers look for evidence of IgE sensitization in blood samples collected from the general population, recognizing that this type of study could overestimate the prevalence rate of a food allergen, because some of the sensitized individuals might not be allergic individuals. Other "Medium" scored data may include robust epidemiological data from other countries or geographical areas. See Table 6 for examples of historical information that we generally intend to score as "Medium." "Medium" prevalence data may also be scored in certain cases as "Low" based on the study quality and representativeness of the data.

As shown in Table 6, we generally intend to score as "Low":

- Prevalence estimations based on sensitization rates or other clinical parameters from selected U.S. populations (e.g., clinical center patient populations, individuals presenting to local or regional hospital systems);
- Surveys based on retrospective review of patient medical records with diagnosis codes related to food allergy, because such diagnosis codes are not always specific for IgE-mediated food allergy; and
- Surveys based on review of frequency of IgE-mediated food allergic reactions in community reports from surveillance databases, because such reports usually do not contain sufficient information to understand the baseline frequency (or denominator) of allergy to the food in the population of reporters.

Consideration of prevalence GRADE data above may also be supplemented by consideration of supplemental data or factors. For example, because some foods may cause both IgE- and non-IgE-mediated reactions, robust prevalence data on non-IgE-mediated allergic reactions or other types of adverse immune-mediated health consequences associated with the food may further complement the IgE-mediated prevalence data and help strengthen the overall public health prevalence score of the food in question.

3. Factor #3: Severity of IgE-mediated food allergic reactions

We recommend that any request for us to evaluate a food or component of food as a food allergen of public health importance include severity data with a score of "High" or "Medium" as shown in Table 6.

Any food allergen has potential to cause a wide range of clinical manifestations. These manifestations can involve a single organ system or multiple organ systems and can range from relatively mild reactions (e.g., sneezing) to severe anaphylaxis reactions that can lead to loss of consciousness, asphyxiation, or shock and can require use of epinephrine or lead to hospitalization or death. We generally intend to use the GRADE system shown in Table 7 when we evaluate:

- The actual severity of the IgE-mediated food allergic reaction;[31] and
- The relative number and frequency of severe reactions.

To evaluate the actual severity of reported reactions to the food allergen, we generally intend to give the greatest weight to the following types of data regarding allergic signs or symptoms:

- Objective signs, in well-characterized allergic individuals, that are confirmed by a physician as IgE-mediated, classified according to scientifically accepted classification system, and treated;

[31] Since some foods may cause both IgE- and non-IgE-mediated reactions, we may consider severity of non-IgE-mediated reactions (e.g., severe diarrhea associated with celiac disease) as supplemental evidence in evaluating overall severity.

- Documented reports of fatality[32] after exposure to the food allergen;
- Objective signs, in well-characterized allergic individuals, elicited by a food challenge study; and
- Objective signs that are typical of allergic reactions and reported in community reports from well-characterized or self-reported allergic individuals.

We generally intend to score as "Low" atypical and/or poorly described objective signs by self-reported or well-characterized allergic individuals in community reports, as well as subjective symptoms in self-reported or well-characterized allergic individuals elicited by food challenge study (see Table 6).

In evaluating the relative number and frequency of severe reactions to the food allergen, we generally intend to give the greatest weight to evidence demonstrating that:

- The food causes a high number or frequency of anaphylaxis or other severe IgE-mediated food allergic reactions per allergic individual or per population of allergic individuals;
- Reactions cause a high number or frequency of serious public health sequalae (e.g., hospital visits), including evidence of fatality; and
- Reactions cause high frequency of comorbidity, including negative patient-centered impacts on quality of life.

4. Factor #4: Allergenic potency

We recommend that any request for us to evaluate a food or component of food as a food allergen of public health importance include potency data with a score of "High" or "Medium" as shown in Table 6. However, we recognize that there could be circumstances in which there will be minimal potency information – e.g., if a food allergen that causes IgE-mediated reactions has a relatively short consumption history and there has not been enough time to design and execute potency studies.[33]

We generally intend to score as "High" allergen potency data obtained from: (1) prospectively designed scored food challenge studies with a wide range of doses to determine threshold EDs in adequate numbers of randomly selected well-characterized allergic individuals; or (2) quantitative risk modeling studies of threshold EDs to food(s) in a population(s) of well-characterized allergic individuals (see Table 6). In evaluating such potency data, we generally intend to give the greatest weight to:

[32] We generally intend to score a report of a fatality after exposure to the food allergen as "High" when the reported fatality occurred in a well-characterized allergic individual and as "Medium" when there is insufficient information to confirm that the fatality occurred in a well-characterized allergic individual (see Table 6).

[33] Challenge studies to evaluate the potency of a food allergen generally are conducted as part of a clinical research study, rather than as a part of the doctor diagnosis of food allergy for individual patients. Thus, potency data are generally less available than data on prevalence and severity.

- Data that provide EDs causing reactions at the mean population level (ED50) and those causing reactions in the most sensitive populations (ED1, ED5, or ED10) to allow comparisons with major food allergens; and
- Data allowing assessment of severity dose-response relationship (e.g., gradient of severity of IgE-mediated food allergic reactions) at the individual or population levels; robust evidence may include information on the relative severity of IgE-mediated food allergic reactions at different ED levels, which would enable us to identify foods with a high probability of severe reactions from low dose exposures.

We generally intend to score as "Medium" allergen potency data obtained from case or community reports describing reactions to quantitatively estimated doses (amounts) of food allergen, derived from information detailing the amount of food product likely consumed during a reaction multiplied by the known or analyzed concentration (e.g., ppm) of food allergen in that food product, in self-reported or well-characterized allergic individuals (see Table 6).

We generally intend to score as "Low" allergen potency data obtained from case or community reports describing reactions to qualitatively estimated doses (amounts) of allergen in self-reported or well-characterized allergic individuals (see Table 6).

In evaluating the public health importance of a food allergen based on the identified body of evidence:

- We generally intend to give the greatest weight to evidence that there is a high probability of severe reactions from low dose exposures, because the probability for adverse health consequences from inadvertently consuming these foods at relatively minor food use levels is greater.
- We also will consider the extent to which processing of the food allergen (or of food containing the food allergen) is known to impact the potency of the food allergen (e.g., if foods containing the food allergen are commonly cooked and cooking the food allergen, or food containing the food allergen, reduces the frequency dose-response or severity dose-response).

B. FDA's Evaluation of Information Relevant to the Labeling and Production of Food Containing a Food Allergen

When we determine whether to evaluate if a food allergen is of public health importance, we may seek or request data and other information relevant to the labeling and production of food containing the food allergen, similar to the data and other information we requested for sesame. Examples of such data and other information are:

- Data and other information relevant to the prevalence in the United States of food allergic reactions that could be attributed to exposure to the food allergen that is not disclosed on the label of food products;
- Prevalence and amounts of the undisclosed food allergen in foods;
- Characteristics of food products and food production practices;

- Data from patient-centered studies or other patient-centered information (e.g., food allergy quality-of-life questionnaires) regarding patients' experiences, perspectives, needs, and priorities regarding avoidance of foods that are or contain food allergens; and
- Data on clinically cross-reactive food allergies to the food and, if relevant, whether potential cross-reactivity to the food allergen would not be well-recognized in the U.S. allergic population.

C. How FDA Intends to Consider the Total Body of Evidence

We generally intend to evaluate whether an IgE-mediated food allergen is of public health importance:

- By considering the prevalence, severity, and potency of the food allergen (Factors #2, #3, and #4) on a case-by-case basis,[34] including supplemental data regarding additional immune-mediated mechanisms; and
- When applicable, by considering additional data and information regarding:
  - The prevalence in the United States of food allergic reactions that could be attributed to exposure to the food allergen that is not disclosed on the label of food products;
  - Prevalence and amounts of the food allergen in foods that is not disclosed on the label of food products;
  - Characteristics of food products and food production practices;
  - Patient-centered studies or other patient-centered information; and
  - Clinically cross-reactive food allergies to the food and, if relevant, whether potential cross-reactivity to the food allergen would not be well-recognized in the U.S. allergic population.

VII. Interested Party Submission of a Citizen Petition

Any interested party may submit a citizen petition under 21 CFR 10.30 asking us to evaluate the public health importance of a non-listed food allergen. In a citizen petition, we recommend that petitioners identify and evaluate the body of evidence applicable to each of the scientific factors listed in section IV of this guidance document as described in section V of this guidance. Petitioners should also provide other information, such as the information relevant to the labeling and production of food containing a food allergen as described in section VI.B of this guidance document, when such information is available and relevant to the food allergen.

[34] The number of permutations regarding scientific factors #2, #3, and #4 is quite large. For example, the prevalence and potency of a food allergy could be high, low, or unknown, and the severity of an IgE-mediated food allergic reaction could be mild, moderate, or severe.

VIII. References

The following references marked with an asterisk (*) are on display at the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852, 240-402-7500, and are available for viewing by interested persons between 9 a.m. and 4 p.m., Monday through Friday; they also are available electronically at https://www.regulations.gov. References without asterisks are not on public display at https://www.regulations.gov because they have copyright restriction. Some may be available at the website address, if listed. References without asterisks are available for viewing only at the Dockets Management Staff. Although FDA verified the website addresses in this document, please note that websites are subject to change over time.

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IX. Appendix A – Additional Considerations

A. "Community Reports" Regarding Food Allergens

For the purpose of this guidance, we use the term "community report" to mean a report, regarding a known or suspected food allergen in a food product, that is submitted to a surveillance database, a research query, or other request for information (e.g., through a notice published in the *Federal Register*), or that is otherwise collected and described (e.g., as a patient case study or a diagnostic food challenge study reported in the scientific literature). A community report can be submitted or prepared by consumers (i.e., be a "self-report"), health care professionals, industry, researchers, government agencies, non-government agencies, or other interested parties. Some community reports (e.g., adverse event reports, case studies) describe an allergic reaction experienced by an individual to a food product, whereas other community reports (usually called product complaints) call FDA's attention to a potential problem or concern (e.g., labeling that does not disclose a food product is or contains a food allergen).

- Examples of surveillance databases are:
  - CAERS,[35] which collects information on:
    - Adverse events regarding FDA-regulated products (e.g., an allergic reaction to a food product[36]); and
    - Product complaints regarding FDA-regulated products (e.g., complaints about products that do not appropriately declare a major food allergen as required by

[35] Information is submitted to CAERS through FDA's MedWatch system (https://www.fda.gov/safety/medwatch-fda-safety-information-and-adverse-event-reporting-program) or to FDA regional offices.

[36] For example, consumers sometimes report an allergic reaction to a food product that contains an undeclared major food allergen that was not added to a food product as an ingredient, but is nonetheless present in the food product, possibly due to allergen cross-contact during production of the food product. Consumers also sometimes report an allergic reaction to a food that is or contains a food allergen that is not a major food allergen.

the FD&C Act or that do not disclose the presence of a food allergen that is not a major food allergen[37]).

- Anaphylaxis registries, such as the European Anaphylaxis Registry (Ref. 42) and the Norwegian Food Allergy Register (Ref. 43), which collects information on specifics of serious allergic reactions to foods occurring in patients who present to regional medical centers.

- An example of a query is a questionnaire asking consumers to report allergies to a specific food or food product, or adverse events experienced with a specific food or food product (e.g., as part of systematic survey to understand prevalence or other scientific questions related to food allergy in a population of patients or consumers). For example, in 2005, researchers in the United Kingdom issued a questionnaire to 400 persons who had reported allergic reactions to sesame (Ref. 44).
- An example of another request for information is a notice published in the *Federal Register* in which FDA invites the public to submit data or other information regarding food allergies or allergic reactions (see, e.g., "Sesame as an Allergen; Notice; Request for comments" (*Federal Register* of October 30, 2018; 83 FR 54594)).[38]

B. Codex Criteria for Evaluating the Public Health Importance of Food Allergens

In 1999, the World Health Organization of the United Nations convened a Food Allergens Labelling Panel to provide guidance to a Joint Expert Committee on Food Additives (JECFA), which provides scientific recommendations to the Codex Alimentarius Commission (Codex) relating to food additives and ingredients in foods. The Food Allergens Labelling Panel was asked to provide guidance on the following issues related to food allergies and intolerances:

- Identifying criteria for adding substances to the Codex list of common allergenic foods, if found to be necessary;
- Developing criteria for identifying products of foodstuffs on the Codex list for which labeling of the food source is not necessary; and
- Considering ways in which FAO and WHO could provide guidance to JECFA on a continuing basis.

In June 1999, Codex adopted a priority list of those foods or food products whose presence should always be declared in the list of ingredients on a food label, because of their allergenic properties (Ref. 25). This priority list included:

[37] For example, some product complaints call our attention to food products that do not disclose the food allergen source of a food allergen that is not a major food allergen. Other product complaints call our attention to food products that do not disclose a food allergen that is not a major food allergen as an ingredient because our food labeling regulations allow the food allergen to be declared with a collective term such as "spice" or "flavoring."

[38] For example, the notice asked stakeholders to submit data and other information about prevalence of allergies and allergic reactions due to sesame in the United States directly to the docket established for the notice. However, our communications about the notice also directed the public to submit individual adverse event reports due to sesame to CAERS rather than to the docket established for the notice.

- Cereals containing gluten[39] and products of these;
- Crustacea and products of these;
- Egg and egg products;
- Fish and fish products;
- Peanuts, soybeans, and products of these;
- Milk and milk products (lactose included);
- Tree nuts and nut products; and
- Sulfites in concentrations of 10 mg/kg or more.

With respect to criteria for the addition of foodstuffs to the Codex priority list of common allergenic foods, the Food Allergens Labelling Panel recommended that the following criteria (the 1999 Codex criteria) be applied:

- The existence of a credible cause-and-effect relationship based upon positive double-blind, placebo-controlled food challenge or unequivocal reports of reactions with typical features of severe food allergy or intolerance reactions.
- There should be reports of severe systemic reactions following exposure to the foodstuff.
- Whereas the Food Allergens Labelling Panel recognized the ideal criterion would be prevalence data in children and adults, supported by appropriate clinical studies, i.e., a double-blind, placebo-controlled food challenged from the general population of several countries, it noted that currently such information was only available for infants, in some countries, and for some foodstuffs. Such information is rarely available for adults. As an alternative, the Food Allergens Labelling Panel agreed that the use of such available data (e.g., comparative prevalence of the specific food allergy in groups of allergy patients from several countries backed up ideally by a double-blind, placebo-controlled food challenge) would be appropriate.

In 2019, the Codex Committee on Food Labeling asked for FAO/WHO to convene an expert consultation to request from FAO/WHO scientific advice relating to the Codex priority list of common allergenic foods, including whether the published criteria for assessing additions and exclusions to the list is still current and appropriate and, subject to the advice from FAO/WHO on the criteria, whether there are foods and ingredients that should be added to or deleted from the list, clarification of the groupings of foods and ingredients in the list, and whether certain

[39] FAO/WHO originally defined this food group as "cereals containing gluten (i.e., wheat, rye, barley, oats, spelt or their hybridized strains) and their products." For cereals containing gluten other than wheat, FALCPA directed us to conduct rulemaking to define, and permit use of, the term ''gluten-free'' on the labeling of foods. On August 5, 2013, FDA issued a final rule defining "gluten-free" for food labeling, which is intended to help consumers, especially those living with celiac disease, be confident that items labeled "gluten-free" meet a defined standard for gluten content (78 FR 47154). FDA defined gluten-containing grains as wheat, rye, and barley. "Gluten-free" is a voluntary claim that can be used by food manufacturers on food labels if they meet all the requirements of the regulations. On August 13, 2020, FDA issued a final rule that establishes compliance requirements for the gluten-free labeling of fermented or hydrolyzed foods such as yogurt, sauerkraut, pickles, cheese, green olives, FDA-regulated beers and wines (e.g., generally those with less than 7 percent alcohol), and hydrolyzed plant proteins used to improve flavor or texture in processed foods such as soups, sauces, and seasonings (85 FR 49240). The gluten-free labeling regulation can be found at 21 CFR 101.91.

foods and ingredients, such as highly refined foods and ingredients, that are derived from the list of foods known to cause hypersensitivity can be exempted from mandatory declaration (Ref. 45).

Starting in late November 2020, FAO/WHO held an expert consultation to address these questions. In April 2022, FAO/WHO issued an Expert Committee report, entitled "Part 1: Review and validation of Codex Alimentarius priority allergen list through risk assessment." This report identified "prevalence of the immune-mediated hypersensitivity to a specific food, severity (i.e., proportion of severe objective reactions to a food/ingredient such an anaphylaxis), and the potency of food/ingredient (i.e., the amount of the food/ingredient required to cause objective signs) as the three key criteria that should be used to establish the priority allergen list" (Ref. 30). The Expert Committee considered global evidence of prevalence, severity, and potency as criteria in reassessing which 1999 priority list foods should remain on the Codex list. As an example, each of the "cereals containing gluten" on the 1999 Codex priority list (which included wheat, rye, barley, and oats) was individually assessed based on these criteria. Because both IgE-mediated food allergies and celiac disease were considered in developing the 1999 Codex priority list, the same endpoints were considered in assessing whether and which of these cereals should remain on the priority list. The Expert Committee found that evidence was available for wheat, rye, and barley to meet key criteria for inclusion on the updated Codex priority list, while insufficient evidence was available for oats.[40]

C. Development of Other Examples of Criteria for Evaluating the Public Health Importance of Food Allergens

Scientific reviews and opinion papers from research groups or organizations have suggested revisions to the 1999 Codex criteria. For example, in 2008, the International Life Sciences Institute-Europe (ILSI-EU) recommended revising the 1999 Codex criteria (Ref. 26). The ILSI-EU revised criteria included "clinical issues (diagnosis, potency of allergen, severity of reactions), population elements (prevalence, exposure), and modulating factors (food processing)." In addition to suggesting revised criteria, ILSI-EU also provided a framework for evaluating whether a food allergen other than those included in the 1999 Codex list of common allergenic foods warranted regulation (e.g., labeling requirements) by weighting the available data according to quality, using a ranking derived from evidence-based medicine (Ref. 26). ILSI-EU and others subsequently evaluated the application of the revised criteria (Ref. 28 and Ref. 29). One publication concluded that the revised criteria were helpful in assessing known food allergens and excluding the food substances associated with non-IgE-mediated hypersensitivity reactions and that the framework for weighting the available data according to quality discriminated between publications that provided high, moderate, and low quality of evidence (Ref. 28). The other publication concluded that the revised criteria presented a way forward for the identification of food allergens of public health importance and for prioritization

[40] The Expert Committee found that wheat should remain on the Codex priority list because of robust data on prevalence, severity, and potency of wheat-mediated IgE-mediated food allergies (in addition to criteria for celiac disease). Rye and barley were found to show weak evidence of causing IgE-mediated food allergic reactions but were determined to remain on the Codex priority list because of key criteria showing these foods responsible for causing severe reactions in celiac disease. Oats were recommended by the Expert Committee to be excluded from the Codex priority list because of a lack of key criteria data showing this food to be a prevalent or important cause of IgE-mediated food allergies or celiac disease.

of allergen risk management and future data gathering (Ref. 29). Another publication applied a risk analysis cycle to food allergy and parameters for hazard scaling (Ref. 27).

In addition, some national regulatory/public health agencies (e.g., Health Canada (Ref. 46) and Food Standards Australia New Zealand (Ref. 47)) have developed or described criteria or types of evidence required to establish new or priority food allergens of public health importance. These criteria have largely mirrored the 1999 Codex criteria.

D. Report of the National Academies of Sciences, Engineering, and Medicine on Food Allergy

In 2016, NASEM issued a report entitled "Finding a Path to Safety in Food Allergy: Assessment of the Global Burden, Causes, Prevention, Management and Public Policy" (Ref. 2). One recommendation in the report was that "…public health authorities in individual countries decide on a periodic basis about which allergenic foods should be included in their priority lists based on scientific and clinical evidence of regional prevalence and severity of food allergies as well as allergen potency" (Ref. 2). The recommendations in the NASEM report focus on IgE-mediated food allergies, which have better defined underlying cellular mechanisms and physiological reactions.