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Guidance for Industry

Assessing the Effects of Significant Manufacturing Process Changes, Including Emerging Technologies, on the Safety and Regulatory Status of Food Ingredients and Food Contact Substances, Including Food Ingredients that are Color Additives

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Food Safety and Applied Nutrition

June 2014

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Guidance for Industry[1]

Assessing the Effects of Significant Manufacturing Process Changes, Including Emerging Technologies, on the Safety and Regulatory Status of Food Ingredients and Food Contact Substances, Including Food Ingredients that Are Color Additives

I. Introduction

This document provides guidance to manufacturers of food ingredients and food contact substances (FCSs), and end users[2] of food ingredients and FCSs, including food ingredients that are color additives. In the remainder of this document, we use the term "food substance" as a general term addressing food ingredients and FCSs.

This guidance is intended to describe the factors you should consider when determining whether a significant change in manufacturing process for a food substance already in the market:

- Affects the identity of the food substance;
- Affects the safety of the use of the food substance;
- Affects the regulatory status of the use of the food substance; and
- Warrants a regulatory submission to FDA.

The manufacturing process for a food substance may evolve, for example, to use a more efficient catalyst, to replace an expensive solvent with a more cost-effective solvent, or to introduce a treatment to reduce the presence of contaminants such as lead. Some of these changes in a manufacturing process may be considered significant, and it is these significant changes in manufacturing process that are the subject of this guidance (some examples of significant changes in manufacturing process are provided in section IV.A. below).

[1] This guidance has been prepared by the Office of Food Additive Safety in the Center for Food Safety and Applied Nutrition at the U.S. Food and Drug Administration.

[2] An end user is a person who uses a food substance in the manufacture of a food product, and who may or may not manufacture the food substance.

This guidance provides our current thinking regarding considerations for assessing the impact of a significant manufacturing process change on the safety and regulatory status of a food substance. In addition, the guidance provides relevant recommendations for assessing the effect of a significant manufacturing process change on the safety and regulatory status of food substances, including those that are the subject of a food additive or color additive regulation, a food contact substance notification, or a generally recognized as safe (GRAS) determination.

As with all food substances, this guidance also is intended to recommend that you consult with us regarding a significant manufacturing process change for a food substance already in the market, irrespective of your conclusion about whether that change affects the safety or regulatory status of the food substance. It is prudent practice for you to do so, particularly when the manufacturing process change involves emerging technologies, such as nanotechnology. Food substances may be used in a wide array of products manufactured, distributed and sold at retail by a large number of firms. The consequences (to consumers and to the food industry) of broadly distributing a food substance that is later recognized to present a safety concern have the potential to be significant.

Any manufacturing change has the potential to be significant, and this remains true for changes or novel products, involving nanotechnology. Emerging technologies such as those that intentionally alter a food substance's particle size distribution on the nanometer scale,[3] which alter the physical and/or chemical properties of food substances, can sometimes be significant manufacturing changes. The discussion in this document of nanotechnology[4] -- in particular, intentional alterations of particle size distribution on the nanometer scale -- primarily addresses circumstances in which there has been a manufacturing change to a food substance already used in food.

FDA recognizes that conventionally manufactured food substances can sometimes include particles with size distributions that extend into the nanometer range. This guidance is not intended to bring into question the regulatory status of such products if they have already been

[3] For the purpose of this document the terms nanometer scale and nanometer range refer to any particle size between 1 nanometer and 1 micrometer.

[4] Nanotechnology allows scientists to work on the scale of molecules to create, explore, and manipulate the biological and material worlds measured in nanometers, one-billionth of a meter. In July of 2007, we issued a report prepared by our Nanotechnology Task Force (Ref. 1).

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

determined to be GRAS or have been approved in response to a food additive petition, color additive petition, or food contact notification.

This guidance is not intended as a premarket guidance document to address data recommendations to support the safety of uses of food substances, or to address the data and information required to support new food additives or new uses of food substances already in the market. FDA has previously released, and periodically updates, guidance documents that address data recommendations to support the safety of uses of food substances not previously authorized. These previously-released guidances are:

- Guidance for Industry - Recommendations for Submission of Chemical and Technological Data for Direct Food Additive Petitions (Ref. 3);
- Guidance for Industry - Color Additive Petitions. FDA Recommendations for Submission of Chemical And Technological Data On Color Additives For Food, Drugs Or Cosmetics (Ref. 4); and
- Guidance for Industry - Preparation of Premarket Submissions for Food Contact Substances: Chemistry Recommendations (Ref. 5).

These documents are available on FDA's Web site. We recommend that manufacturers consult these guidance documents before preparing a submission to FDA. The discussions and recommendations in this guidance document regarding appropriate pathways to gain premarket review by FDA may also be applicable to new uses of food substances.

This guidance is not applicable to other products regulated by FDA, including over-the-counter and prescription drugs and medical devices. FDA's current thinking concerning nanomaterials for food uses, which is explained below, is not intended to provide guidance to manufacturers or end users about the use of nanomaterials in any non-food article regulated by FDA. This guidance is also not intended to provide guidance to manufacturers or end users of color additives intended for use in non-food products (e.g., products that are cosmetics, drugs or medical devices).

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. Regulatory Framework for Food Substances

To give context to FDA's guidance, this section provides an overview of the regulatory framework that applies to food substances subject to this document. Under the Federal Food, Drug, and Cosmetic Act (the FD&C Act), some food substances may require premarket review and approval by FDA. Other food substances, however, may only require premarket notification to FDA. In yet other circumstances, the FD&C Act does not require either premarket review or premarket notification. FDA's guidance regarding the effects of significant manufacturing process changes is informed by these various requirements.

A. Industry's Responsibility Regarding the Safe and Lawful Use of Food Substances

Under section 402 of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) [21 U.S.C. § 342], food shall be deemed to be adulterated if, among other things:

- The food bears or contains an added poisonous or deleterious substance which may render it injurious to health (section 402(a)(1) of the FD&C Act);
- The food bears or contains any food additive that is unsafe within the meaning of section 409 of the FD&C Act [21 U.S.C. § 348] (section 402(a)(2)(C) of the FD&C Act); or
- The food bears or contains a color additive that is unsafe within the meaning of section 721(a) of the FD&C Act [21 U.S.C. § 379e(a)] (section 402(c) of the FD&C Act).

Under section 301 of the FD&C Act [21 U.S.C. § 331], the following acts (among others) and the causing thereof are prohibited:

- The introduction or delivery for introduction into interstate commerce of any food that is adulterated (section 301(a) of the FD&C Act);
- The adulteration of any food in interstate commerce (section 301(b) of the FD&C Act); and
- The receipt in interstate commerce of any food that is adulterated, and the delivery or proffered delivery thereof for pay or otherwise (section 301(c) of the FD&C Act).

Under sections 402 and 301 of the FD&C Act, it is the responsibility of both the manufacturer and the end user of a food substance to ensure that the use of the food substance is safe and lawful. Remedies for violations of the FD&C Act include seizure, injunction, and criminal prosecution.[5]

B. Food Additive Statutory and Regulatory Provisions

In 1958, Congress enacted the Food Additives Amendment to the FD&C Act; in 1997, Congress enacted the Food and Drug Administration Modernization Act (FDAMA) as another amendment to the FD&C Act. Briefly, the Food Additives Amendment and FDAMA:

- Define the term "food additive" (section 201(s) of the FD&C Act) [21 U.S.C. § 321(s)] to:
    - Broadly include any substance, the intended use of which results or may reasonably be expected to result, directly or indirectly, in its becoming a component or otherwise affecting the characteristics of food; and
    - Exclude (among other things) substances that are generally recognized, among experts qualified by scientific training and experience to evaluate their safety ("qualified experts"), as having been adequately shown through scientific procedures (or, in the case of a substance used in food prior to January 1, 1958, through either scientific procedures or through experience based on common use in food) to be safe under the conditions of their intended use;

[5] See, e.g., sections 301(a) through (c) and section 303(a) of the FD&C Act.

- Establish a premarket approval process for food additives and for food contact substances, whether or not they are food additives (sections 409(b) - (h) of the FD&C Act);
- Provide that food shall be deemed to be adulterated if it is, or bears or contains, any food additive that is unsafe within the meaning of section 409 of the FD&C Act (section 402(a)(2)(C) of the FD&C Act)[6];
- Establish that a food additive shall, with respect to any particular use or intended use of such additive, be deemed to be unsafe for the purposes of the application of section 402(a)(2)(C) of the FD&C Act unless:
    - It and its use or intended use conform to the terms of an exemption which is in effect pursuant to section 409(j) of the FD&C Act (section 409(a)(1) of the FD&C Act);
    - There is in effect, and it and its use or intended use are in conformity with, a regulation issued under section 409 of the FD&C Act prescribing the conditions under which such additive may be safely used (section 409(a)(2) of the FD&C Act); or
    - In the case of a food additive that is a FCS, there is:
        - in effect, and such substance and the use of such substance are in conformity with, a regulation issued under section 409 of the FD&C Act prescribing the conditions under which such additive may be safely used (section 409(a)(3)(A) of the FD&C Act); or
        - a notification submitted under section 409(h) of the FD&C Act that is effective (section 409(a)(3)(B) of the FD&C Act).
- Provide that while a regulation relating to a food additive, or a notification under section 409(h)(1) of the FD&C Act relating to a food additive that is a FCS, is in effect, and has not been revoked pursuant to section 409(i) of the FD&C Act, a food shall not, by reason of bearing or containing such a food additive in accordance with the regulation or notification, be considered adulterated under section 402(a)(1) of the FD&C Act.

A food substance is not subject to the premarket approval requirements of section 409 of the FD&C Act if its safety is generally recognized by qualified experts (section 201(s) of the FD&C Act). A determination that a particular use of a substance is GRAS (unless established by common use prior to 1958) requires both technical evidence of safety and a basis to conclude that this technical evidence of safety is generally known and accepted (i.e., general recognition of safety). See 21 CFR 170.30. In contrast, a determination that a particular use of a food additive is safe via premarket approval requires only technical evidence of safety.

Thus, "a GRAS substance is distinguished from a food additive on the basis of the common knowledge about safety of the substance for its intended use, rather than on the basis of what the substance is or the types of data and information that are necessary to establish its safety" (62 FR 18938 at 18940; April 17, 1997). "To establish [general] recognition, the proponent must show that there is a consensus of expert opinion regarding the safety of the use of the substance" (62 FR at 18939).

[6] The term "safe," as used in section 201(s) of the FD&C Act and in the sections relevant to this document (sections 409 and 721 of the FD&C Act) refers to the health of man or animal (section 201(u) of the FD&C Act).

Regulations identifying GRAS conditions of use for certain substances in food are in Part 182 and regulations affirming the GRAS status of the use of some food substances are in 21 CFR Parts 184 and 186, respectively. Regulations prescribing conditions under which substances affirmed as GRAS may be safely used in food predicate usage under conditions of good manufacturing practice (GMP) (21 CFR 182.1(b) and 184.1(b)). A food substance that is identified or affirmed as GRAS must also meet the requirements in 21 CFR 170.30(h).

Under the Food Additives Amendment, a food substance that is GRAS for a particular use may be marketed for that use without our review and approval. However, when a use of a food substance is not GRAS (and other exclusions provided under section 201(s) of the FD&C Act, such as for a pesticidal substance (section 201(s)(2) of the FD&C Act), are inapplicable), that use of the substance is a food additive use subject to the premarket approval mandated by the FD&C Act. Where a use of such a food substance is marketed without premarket approval we can take enforcement action to stop distribution of the food substance and foods containing that food substance on the grounds that such foods are adulterated because they are or contain an unlawful food additive.

We have established regulations defining terms associated with food additives, food contact substances, and substances that are GRAS (21 CFR 170.3). Under 21 CFR 170.3(i), "safe" or "safety" means that there is a reasonable certainty in the minds of competent scientists that the substance is not harmful under the intended conditions of use. This definition of "safe" or "safety" provides that it is impossible in the present state of scientific knowledge to establish with complete certainty the absolute harmlessness of the use of any substance. Under the regulatory framework, safety may be determined by scientific procedures or by general recognition of safety. In determining safety under either route, the following factors shall be considered:

- The probable consumption of the substance and of any substance formed in or on food because of its use (21 CFR 170.3(i)(1));
- The cumulative effect of the substance in the diet, taking into account any chemically or pharmacologically related substance or substances in such diet (21 CFR 170.3(i)(2)); and
- Safety factors which, in the opinion of experts qualified by scientific training and experience to evaluate the safety of food and food substances, are generally recognized as appropriate (21 CFR 170.3(i)(3)).

Regulations prescribing conditions under which substances approved as food additives, listed as GRAS, or affirmed as GRAS may be safely used predicate usage under conditions of good manufacturing practice (21 CFR 172.5, 182.1(b), 184.1(b)), which include the following:

- The quantity of the substance added to food does not exceed the amount reasonably required to accomplish its intended physical, nutritive, or other technical effect in food; and
- Any substance intended for use in or on food is of appropriate food grade and is prepared and handled as a food ingredient.

We have established (or proposed to establish) regulatory submission programs regarding several categories of food substances relevant to section 409 of the FD&C Act. We describe the

principal regulatory submission programs in Appendix 2 of this document. We have provided guidance to industry on administrative aspects of these regulatory submissions (Refs. 6 through 8).

C. Color Additive Statutory and Regulatory Provisions

In 1960, Congress enacted the Color Additive Amendments to the FD&C Act. Briefly, the 1960 Color Additive Amendments:

- Define the term "color additive" (section 201(t) of the FD&C Act);
- Establish a listing and certification process for color additives (sections 721[7](b) - (e) of the FD&C Act);
- Amend the food adulteration provisions of the FD&C Act to deem adulterated any food that is, or bears or contains, any color additive that is unsafe within the meaning of section 721 of the FD&C Act (section 402(c) of the FD&C Act);
- Establish that a color additive shall, with respect to any particular use or intended use of such additive, be deemed to be unsafe for the purposes of the application of section 402(c) of the FD&C Act unless:
    - There is in effect, and such additive and such use are in conformity with, a regulation issued under section 721(b) of the FD&C Act listing such additive for such use, including any provision of such regulation prescribing the conditions under which such additive may be safely used (section 721(a)(1)(A) of the FD&C Act); and
    - Such additive either (i) is from a batch certified, in accordance with regulations issued pursuant to section 721(c) of the FD&C Act, for such use, or (ii) has, with respect to such use, been exempted by the Secretary from the requirement of certification (section 721(a)(1)(B) of the FD&C Act); or
    - Such additive and such use thereof conform to the terms of an exemption which is in effect pursuant to subsection (f) of this section (section721(a)(2) of the FD&C Act); and
- Provide that, while there are in effect regulations under sections 721(b) and (c) of the FD&C Act relating to a color additive or an exemption pursuant to section 721(f) of the FD&C Act with respect to such additive, an article shall not, by reason of bearing or containing such additive in all respects in accordance with such regulations or such exemption, be considered adulterated within the meaning of section 402(a)(1) of the FD&C Act.

There is no GRAS provision for color additives, and all uses of color additives must be approved as safe by FDA prior to marketing.

We have established regulations defining terms associated with color additives (21 CFR 70.3). Under 21 CFR 70.3(i), safe means that there is convincing evidence that establishes with reasonable certainty that no harm will result from the intended use of the color additive.

[7] 21 U.S.C. 379e.

We describe our program for a petition process for color additives in Appendix 2 of this document. We have provided guidance to industry on administrative aspects of the color additive petition process (Ref. 6).

III. Safety Assessment of a Food Substance

As described in our existing guidance documents (Refs. 6 to 11), an assessment of the safety of a food substance generally involves an evaluation of information about its safety and functionality including all studies and tests of a food additive on animals and humans and all studies and tests of a food additive for identity, stability, purity, potency, performance, and usefulness (21 CFR 171.1(h)(4)). We briefly describe each of these aspects in sections III.A through III.D of this document.

Our regulations and guidance documents on food substances generally include the manufacturing process as part of the information describing the identity of a food substance. However, because the purpose of this document is directed to assessing the effect of a change in manufacturing process on the safety and regulatory status of a food substance, in this document we discuss the role of the manufacturing process in a safety assessment in a separate section (see section III.E).

A. Identity

The identity of a food substance is usually described in terms of information such as:

- Its name (including chemical name and a common or trade name);
- Applicable identification number, such as a Chemical Abstracts Service Registry Number (CAS Reg. No.) or an Enzyme Commission Number;
- Applicable chemical formula(e);
- Source (when a food substance is of natural biological origin);
- Quantitative composition;
- Impurities and contaminants; and
- Physical and chemical properties and specifications for these properties (e.g., melting point, boiling point, specific gravity, refractive index, optical rotation, pH, solubility, reactivity, particle size, and chromatographic, spectroscopic or spectrometric data that can be used as a "fingerprint" for identification).

The specifications of identity of a food substance are an important component of the safety assessment and are used to establish safe conditions of use in food. Changes in the physical and chemical properties of a food substance can influence its technical effect in food or food contact materials and can influence the nutritional or toxicological properties of the food substance.

In sections III.B through III.D of this document, we explain how the identity of a substance (particularly its physical and chemical properties) can affect the technical effect, self-limiting levels of use, and dietary exposure and the level at which a food substance exhibits adverse effects.

B. Technical Effect

Substances may be added to food to accomplish a variety of technical effects in food. Examples of food substances that may be added for physical or technical functional effects include antimicrobial agents, humectants, flavoring agents, surface-active agents, stabilizers and thickeners (21 CFR 170.3(o)).

The physical and chemical properties of a food substance generally impact its technical effect and significant changes to a food substance's technical or functional effect may result in conditions of use that are not authorized. For example:

- If an isolated or chemically processed fiber is intended for use as a replacement for part of the flour used in baked goods, its ability to swell due to high water absorption or to bind physiologically important ions may be relevant to determining the appropriate level of the fiber in baked goods.
- The color of a color additive may change simply by reducing the particle size of the substance, as seen with gold particles which display a range of colors dependent on the size of the particle (Ref. 12).

C. Self-limiting Levels of Use

When a substance is added to food above its technologically self-limiting level, the food may become unpalatable, unappealing or otherwise unfit for consumption. For example, the taste associated with many chemically defined flavoring substances limits the levels at which the flavoring substances can be used. A self-limiting level of use can help ensure safety if, for example, any known toxic effects would only occur at levels that exceed the self-limiting use levels.

The physical and chemical properties of a food substance can affect the level at which it becomes self-limiting from a food technology or palatability perspective. For example, the self-limiting level of a flavoring agent may be affected by the particle size of the flavoring agent – e.g., if smaller particles are absorbed more quickly than larger particles. Significant alterations to physical or chemical properties of a food substance and any associated changes to the self-limiting use levels are important considerations in the safety assessment and in establishing the conditions of safe use of the food substance.

D. Dietary Exposure and Safety Studies

Studies conducted *in vitro* or *in vivo* can identify adverse effects that could occur from acute exposure to, or chronic consumption of, a food substance. In most cases, such effects are dose-dependent. A key determinant in the safety evaluation of a food substance is the relation of its probable human intake to the level at which adverse effects are observed in toxicological studies (Ref. 9). In many cases, determining the amount of a food substance that can safely be consumed involves application of a "safety factor" (as described in 21 CFR 170.3(i)) to a "no observed adverse effect level" for the most sensitive indicator of an observed adverse effect.

Alterations in the physical and chemical properties of a food substance can affect its bioavailability through altered absorption, distribution, metabolism and excretion of the substance in the body. Such changes in the substance's biological interactions can affect the level at which toxic effects may occur (Ref. 13). For example, the particle size of a food substance may affect its ability to be absorbed by the body or to migrate from food packaging into food. In such circumstances, safety studies conducted with a food substance manufactured as relatively large particles may have little relevance to the safety of that food substance when manufactured in a substantially smaller particle size.

FDA generally recommends that manufacturers and end users follow our toxicology guidance, (see, e.g., Refs. 10 and 11) when preparing their comprehensive toxicology profile. There are instances where a compound, or a class of compounds, has known toxicological endpoints that are not specifically addressed through the standard guidelines, e.g., the potential risk of alloimmunization[8] posed by exposure to human proteins. In such cases, it is the responsibility of manufacturers and end users to develop appropriate protocols to address particular safety issues. Historically, such persons have been advised that they should consult with FDA on the safety issues related to the intended use.

E. Manufacturing Processes, including Nanotechnology

The manufacturing process of a food substance is considered for the purposes of safety assessment only insofar as it may affect the properties and safety of the finished product. As explained below, the manufacturing process may affect the identity of the food substance or its conditions of use. The manufacturing process may also affect the purity of a food substance, such as the amounts of impurities and contaminants in the food substance. For example:

- An enzyme preparation that is manufactured from an animal source and contains the enzyme chymosin as its principal enzyme component (§ 184.1685(a)(1)) is chemically different from an enzyme preparation that is manufactured from a microbial source and contains the enzyme chymosin as its principal enzyme component (§ 184.1685(a)(2)). Although they both contain an enzyme component that catalyzes the same chemical reaction, they also contain distinctly different constituents derived from the production organism and constituents derived from the manufacturing process (e.g., components of the fermentation media or the residues of processing aids).
- Including an activated carbon treatment of fish oil can reduce levels of polycyclic aromatic hydrocarbons (PAHs) that can be present in fish oil obtained from fish from a natural marine environment (Ref. 14).
- The catalyst for the production of a food contact polymer may affect the chemical identity or the amounts of residual contaminants that may migrate from the polymer to food.
- The particle size distribution of a food substance may affect its ability to be absorbed by the body or to migrate from food packaging into food (Ref. 13).

[8] Alloimmunization is an immune response generated in an individual or strain of one species by an alloantigen from a different individual or strain of the same species (Dorland's Online Medical Dictionary for Health Consumers. © 2007; available online at: http://encyclopedia.thefreedictionary.com/alloimmunization)

Nanotechnology is an emerging technology that can be used in food manufacturing. The application of nanotechnology may result in product attributes that differ from those of conventionally-manufactured products, and thus may merit particular examination. However, FDA does not categorically judge all products containing nanomaterials or otherwise involving application of nanotechnology as intrinsically benign or harmful. Rather, for nanotechnology-derived and conventionally-manufactured food products alike, FDA considers the characteristics of the finished product and the safety of its intended use.

FDA issued a guidance document to industry on the agency's considerations related to nanotechnology applications in FDA-regulated products (Ref. 2). Consistent with the agency's guidance, in this document, we are providing guidance to industry on the potential impact of significant manufacturing process changes involving nanotechnology on the safety and regulatory status of food substances. FDA's consideration of nanotechnology applications in food substances in this document is consistent with the agency's guidance (Ref. 2) and with the broader federal guidance on regulatory oversight of emerging technologies (Ref. 15) and nanotechnology (Ref. 16).

In this section, we discuss nanotechnology -- in particular, intentional alterations of particle size distribution on the nanometer scale -- to address circumstances in which there is a manufacturing change to a food substance already used in food. FDA considers food manufacturing processes that involve nanotechnology in the same manner as any other food manufacturing technology. Although traditionally manufactured food substances can sometimes include particles with size distributions that extend into the nanometer range, recent advances in technology can allow the intentional production of food substances with particle size distributions more fully in the nanometer range, resulting in new properties not seen in traditionally manufactured food substances.

As with any other manufacturing technologies applied to food, nanotechnology and other emerging technologies may introduce issues that warrant additional or different evaluation during a safety assessment of a food substance (Ref. 1). For example, so-called nano-engineered food substances can have substantially altered bioavailability and may, therefore, raise new safety issues that have not been seen in their traditionally manufactured counterparts (Ref. 13). There is debate regarding the appropriate testing to judge the safety of food substances where physical and chemical properties are manipulated by engineering particle size distributions in the nanometer range, in some instances to intentionally manipulate the biological properties, as also noted by some scientific and regulatory authorities (Refs. 1, 13, 17 and 18). Guidance and extrapolation from data on traditionally manufactured food substances can generally be accomplished only on a case-by-case basis.

When a food substance is manufactured to include a particle size distribution shifted more fully into the nanometer range, safety assessments should be based on data relevant to the nanometer version of the food substance. Where nano-engineered food substances have new properties, additional or different testing methods may be necessary to determine the safety of the food substance. For example, particle size, surface area, aggregation/agglomeration, or shape may impact absorption, distribution, metabolism and excretion (ADME) and potentially the safety of the nano-engineered food substance (Refs. 13, 17). In such cases, it may be necessary to further

examine the effects of a change in these properties, including any effects on the bioavailability of the food substance and its transport across the gut.

The variation in biological activity that may result from engineering food substances in the nanometer range may raise questions about the applicability of traditional safety tests for these materials. Thus, as with any studies to support the safety of food substances, studies to establish the safety of food substances manufactured using nanotechnology should have been appropriately validated for these materials. Notably, variability has been reported when traditional toxicity tests have been used to assess nanomaterials (See Refs. 19, 20 related to traditional genotoxicity tests). Because of this variability, and because the physicochemical properties of an individual nanomaterial may require adjustments to a particular assay, validation (single and/or multi-laboratory) of traditional *in vitro* toxicity tests will ensure that the results are meaningful and appropriate to the safety assessment of the nanomaterial food substance. In assuring appropriate validation, FDA anticipates that method validation for nanomaterial food substances would include parameters such as accuracy, precision, sensitivity, specificity, repeatability, and biological relevance. FDA has developed validation criteria for regulatory methods that are used to detect chemicals in FDA-regulated foods (Ref. 21), and these general guidelines would also be useful to demonstrate or confirm that a traditional toxicity text is suitable for testing nanomaterial food substances.

FDA has issued guidance to industry to provide recommendations on chemical and technological data that we consider necessary for the evaluation of food additives, color additives, and food contact substances (Refs. 3 to 5). In those documents, we discuss the relevance of particle size in submitting safety assessments for food additive petitions, color additive petitions, and food contact notifications. We encourage manufacturers to refer to those documents for any questions related to safety data submissions to the agency. FDA continues to welcome consultations with industry as an approach to ensuring that food developed using new technologies will be safe. For example, we encourage developers of new plant varieties developed using modern techniques of biotechnology to consult with us (Ref. 22).

Some Food Contact Notifications (FCNs) (e.g., FCNs 716 and 818) have included information describing the use of a FCS with particle sizes in a nanometer range. To date, we have not received food or color additive petitions, or GRAS affirmation petitions or notices, for any uses of food substances with a particle size distribution fully in the nanometer range.

In summary, safety assessments should be as rigorous as possible and should be based on data relevant to the version of the food substance intended for use. Where safety questions are raised that experts would need additional data to resolve and such data are not generally recognized, the criteria for GRAS would not be satisfied for the use of such food substances. At this time, we are not aware of any food substances intentionally engineered[9] on the nanometer scale for which

[9] As noted in the agency guidance (Ref. 2), in considering applications of nanotechnology, we distinguish between products that have been engineered to contain nanoscale materials or involve the application of nanotechnology from those products that contain incidental levels of nanomaterials or those that contain materials that naturally occur in the nanoscale range. FDA recognizes that conventionally manufactured food substances can sometimes include particles with size distributions that extend into the nanometer range. As indicated above, this guidance is not intended to bring into question the regulatory status of such products to the extent that they may have already been determined to be GRAS or approved in response to a food additive petition, color additive petition, or food

there are generally available safety data sufficient to serve as the foundation for a determination that the use of a food substance is GRAS.

IV. Discussion

A. Considerations for Assessing the Impact of a Significant Manufacturing Process Change on the Safety and Regulatory Status of a Food Substance

Before any food substance is marketed, it is the subject of a safety assessment such as we describe in section III of this document. As technology changes and substitutes for starting materials or aspects of the original manufacturing process become available, the manufacturing process for a food substance may evolve. Some such changes may be significant, and others less so. This guidance document addresses changes in the manufacturing process that are significant. Examples of significant changes in manufacturing process may include:

- A change in one or more starting materials;
- A change in the concentration of starting materials;
- A change in catalyst;
- A change in the source microorganism (including a change in strain) used for a food substance derived from fermentation of a microorganism; and
- A change in food manufacturing or ingredient technology, such as the use of emerging technologies that affect the particle size distribution of a food substance.

We expect that there will be circumstances where a significant manufacturing process change, impacts the safety, the regulatory status, or both, of a food substance. In such circumstances, a new regulatory submission may be necessary to clearly establish the conditions under which the food substance, manufactured by a new process, is safe and lawful. In the case of emerging technologies, a manufacturing process change may alter the identity or intended use of the food substance and a new authorization may be required.

For food substances already in the marketplace, a significant manufacturing process change of the food substance can affect the safety of the food substance. Section III of this document explains some of the ways in which a significant manufacturing process change for a food substance can impact its safety.

A significant manufacturing process change of a food substance already in the market can also affect the identity or conditions of use of a food substance, rendering the use of the food substance not within the scope of a food additive regulation; a GRAS listing or affirmation in our regulations; an effective food contact notification; or an existing determination of GRAS status. When determining whether an existing regulation, FCN, or GRAS determination applies to the use of a food substance that has been subjected to a significant manufacturing process change, it is important to consider the identity and intended conditions of use of the food substance

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contact notification. However, as noted in the text, intentional alterations in particle size distribution on the nanometer scale can sometimes be significant manufacturing changes.

manufactured by the new process in comparison to the identity and intended conditions of use of the food substance that was the subject of the original approval, notification, or determination. For example, the characteristic properties may not match the information considered in a determination of GRAS status, rendering the previous determination of GRAS status inapplicable.

There also may be cases where it simply is not clear whether the use of a food substance complies with an existing regulation. It is prudent practice for manufacturers and end users of food substances to take appropriate steps to ensure that the use of the substance satisfies all regulatory requirements.

Appendix 1 provides three specific examples of situations in which we reconsidered the regulatory status of the use of a food substance and concluded that a significant change in manufacturing process did not negatively impact safety. In these specific examples, we reviewed the data and factual information supporting a conclusion that the intended use of the food substance continued to be safe and lawful after the manufacturing process change.

B. Recommendations for Assessing the Effect of a Significant Manufacturing Process Change on the Safety and Regulatory Status of a Food Substance

1. The use of food substances that are the subject of a food additive or color additive regulation[10]

We recommend that, whenever there has been a significant manufacturing process change for a food substance that is the subject of a food additive or color additive regulation, you:

- Determine what changes have been made to the identity of the food substance as a result of the change in manufacturing process, including its physicochemical structure and properties, purity, and impurities;
- Taking into account any impact of the change in identity of the food substance, conduct a safety assessment for the use of the food substance, including characteristic properties such as physicochemical structure and properties, purity, impurities, bioavailability, or toxicity;
- Consider whether the use of the food substance is authorized under a food additive or color additive regulation. Relevant to such a determination are the identity of the food substance and its conditions of use described in the administrative record for a substance subject to a food additive or color additive regulation. For example, the food substance would not be within the scope of a regulation where:
    - The identity of, manufacturing process for, or the conditions of use of the food substance do not comply with a regulation; or
    - The food substance is not of appropriate food grade as a result of impurities introduced into the food substance by the change in manufacturing process;

[10] These food substances include food contact substances that are the subject of a food additive regulation.

- Consult with us about your conclusions about the impact of the significant manufacturing change on the safety and regulatory status of the use of the food substance; and
- Make an appropriate regulatory submission to FDA as circumstances warrant.

2. The use of food contact substances for which there is an effective Food Contact Notification

Our long-standing guidance to industry on administrative aspects of a food contact notification advises that a new notification should be submitted if substantive changes are made in the specifications for the FCS or if significant changes are made in the manufacturing method that result in substantive changes in the identity of the product or its impurities, and/or levels of impurities (Refs. 5 and 11). Consistent with our previous administrative guidance, in this guidance we recommend that, whenever there has been a significant manufacturing process change for a food contact substance, you:

- Determine what changes have been made to the identity of the food contact substance as a result of the manufacturing process change, including its physicochemical structure and properties, purity, and impurities;
- Taking into account any impact of the change in identity of the food contact substance, conduct a safety assessment for the use of the food contact substance, including characteristic properties such as physicochemical structure and properties, purity, impurities, bioavailability, or toxicity;
- Consider whether the substance would be within the scope of an effective FCN. For example, it would not be within the scope of an effective FCN if:
    - The identity of or the conditions of use of the food contact substance are significantly different from those described in a previously submitted notification; or
    - The food contact substance is no longer of appropriate food grade as a result of impurities introduced into the food contact substance by the change in manufacturing process;
- Consult with us about your conclusions about the impact of the significant manufacturing change on the safety and regulatory status of the use of the food contact substance; and
- Make an appropriate regulatory submission to FDA as circumstances warrant.

Altering the manufacturing process of a notified food contact substance to either produce components in the nanometer scale or increase the proportion of nanometer scale components can sometimes be a significant manufacturing change that could result in a substantive change to the specifications and/or in the identity of the food contact substance or its impurities, and/or levels of impurities. In the event of such substantive change, we advise you to submit a new notification.

3. The use of food substances that are affirmed or identified as GRAS in 21 CFR

We recommend that, whenever there has been a significant manufacturing process change for a food substance that is the subject of a GRAS affirmation or identified as GRAS in our regulations, you:

- Determine what changes have been made to the identity of the food substance as a result of the change in manufacturing process, including its physicochemical structure and properties, purity, and impurities;
- Taking into account any impact of the change in identity of the food substance, conduct a safety assessment for the use of the food substance, including characteristic properties such as physicochemical structure and properties, purity, impurities, bioavailability, or toxicity;
- Consider whether the use of the substance is within the scope of a GRAS affirmation or identification as GRAS in our regulations. Relevant to such a determination are the identity of the food substance and its conditions of use described in the administrative record for a substance affirmed or identified as GRAS. For example, it would not be within the scope of a GRAS affirmation or identification as GRAS when:
    - The identity of, manufacturing process for, or the conditions of use of the food substance are significantly different from those of the substance affirmed or identified as GRAS; or
    - The food substance is not of appropriate food grade as a result of impurities introduced into the food substance by the change in manufacturing process;
- Consult with us about your conclusions about the impact of the significant manufacturing change on the safety and regulatory status of use of the food substance; and
- Make an appropriate regulatory submission to FDA as circumstances warrant.

As the Agency explained in the final rule establishing the GRAS affirmation process, "a regulation affirming the GRAS status of an ingredient, must, under section 201(s) of the FD&C Act, be restricted to the ingredient that has been in common use in food or that was the subject of scientific tests to determine its safety. The burden is on the manufacturer to demonstrate that the ingredient used is of the same composition as the ingredient that has been traditionally used or that has been investigated by researchers." (41 Fed. Reg. 53600, 53604 (Dec. 7, 1976)). Furthermore, if there is a question whether a food substance differs from the food substance identified in the regulation affirming the substance as GRAS because of a change in manufacturing process, "it is the obligation of the manufacturer to demonstrate whether the ingredient has been affirmed as, or is otherwise, GRAS" (41 Fed. Reg. at 53604).

4. Use of a food substance for which there is an existing determination that a use of a food substance[11] is GRAS

Because a significant manufacturing process change can affect the safety, regulatory status, or both of a food substance, we recommend that, whenever there has been a significant manufacturing process change for a food substance that is the subject of a GRAS determination, you:

- Determine what changes have been made to the identity of the food substance as a result of the change in manufacturing process, including its physicochemical structure and properties, purity, and impurities;

[11] As explained in section II.C. above, there is no GRAS provision for color additives and all uses of color additives must be approved as safe by FDA prior to marketing. The reference to "food substance" here does not include food ingredients that are used as color additives.

- Taking into account any impact of the change in identity of the food substance, conduct a safety assessment for the use of the food substance, including characteristic properties such as physicochemical structure and properties, purity, impurities, bioavailability, or toxicity;
- Consider whether the GRAS status of the use of the food substance would be affected – for example, it would not be GRAS if:
    - The identity of, manufacturing process for, or the conditions of use of the food substance are significantly different from those described in a previous GRAS determination;
    - The manufacturing changes are so novel as to preclude general recognition of safety; or
    - The food substance is no longer of appropriate food grade as a result of impurities introduced into the food substance by the change in manufacturing process;
- Consult with us about your conclusions about the impact of the significant manufacturing change on the safety and regulatory status of the use of the food substance; and
- Make an appropriate regulatory submission to FDA as circumstances warrant.

In the specific instance of nanotechnology, a food substance manufactured for the purpose of creating very small particle sizes with new functional properties likely would not be covered by an existing GRAS determination for a related food substance manufactured without using nanotechnology. A determination that a particular use of a substance is GRAS (unless established by common use prior to 1958) requires *both* technical evidence of safety *and* a basis to conclude that this technical evidence of safety is generally known and accepted (i.e., general recognition of safety). At present, for nanotechnology applications in food substances, there are questions related to the technical evidence of safety as well as the general recognition of that safety, that are likely to be sufficient to warrant formal premarket review and approval by FDA, rather than to satisfy criteria for GRAS status[12]. (See, for example, discussion of nanotechnology under "Safety Assessment of a Food Substance" in Section III.E. of this guidance).

As FDA stated in the preamble to the proposed rule for the GRAS notification program, "[T]he published results of a particular safety study may not be sufficient to demonstrate the common knowledge element if the study raises safety questions that require additional data to be resolved" (62 FR at 18943). Similarly, if fundamental questions exist regarding such a study's basic ability to resolve or address relevant safety questions, that study is likely to be insufficient to demonstrate general recognition of safety.

Where an existing GRAS determination does not apply, we note that a separate determination of GRAS status for the use of the food substance would depend both on technical evidence of safety and on general recognition of safety (in other words, this evidence being both generally available and accepted by qualified experts). It is prudent to consult with us on any potential view that the available data and information could form a basis for a determination of GRAS status of a food substance that involves significant manufacturing process changes, including but not limited to those involving nanotechnology or other emerging technologies. Such technologies could be so

[12] See generally footnote 9 above.

new as to preclude a consensus among experts that the use of a food substance manufactured using that technology is safe, thus precluding a determination that the use of the food substance is GRAS. Therefore, it is likely that premarket review and approval of the food substance on a case-by-case basis by the agency is warranted.

V. References

We have placed the following references on display in the Division of Dockets Management, Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. You may see them at that location between 9 a.m. and 4 p.m., Monday through Friday. As of [Month, day, year], FDA had verified the Web site address for the references it makes available as hyperlinks from the Internet copy of this guidance, but FDA is not responsible for any subsequent changes to Non-FDA Web site references after [June 4, 2014].

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Appendix 1. Examples of FDA's Previous Consideration of Manufacturing Process Changes

Below we provide three specific examples where we have already reconsidered the regulatory status of the use of a food substance and concluded that a significant manufacturing process change did not negatively affect safety. The examples below are intended to illustrate how food manufacturing process changes factor into our consideration of effects on identity, safety, and/or regulatory status of resultant food substances. We intend to update these examples as the agency gains additional experience evaluating food substances, including those manufactured using nanotechnology.

A. Carrageenan (21 CFR 172.620)

Under 21 CFR 172.620, carrageenan is described as a "refined hydrocolloid that is prepared by aqueous extraction from specific red seaweeds." Traditionally, carrageenan had been produced by extracting the carrageenan (from one of eight red seaweeds listed in the regulation) and filtering the extract to remove cellulose and other substances. In the late 1970s, a manufacturing change that was developed resulted in less complete removal of cellulose and a less refined product.

Due to limited information about this new process, we initially requested that a new food additive petition be submitted. Upon review of the modified manufacturing process, we determined that the process used to produce the less refined carrageenan met the aqueous extraction requirement in the regulation, the new material conformed to the food ingredient specifications for carrageenan, and the process was as effective at removing impurities normally found in seaweed as the original manufacturing method. We concluded that the only significant difference between the new "carrageenan" and traditional carrageenan is that the former contains

more cellulose compared to traditionally refined carrageenan. We did not consider the additional cellulose in carrageenan to be a safety concern and concluded that the new product still complied with the regulation for carrageenan. In light of this conclusion, we rescinded our earlier request for a food additive petition.

B. Xanthan Gum (21 CFR 172.695 and GRAS Notice No. GRN 000121)

Xanthan gum is approved as a food additive for use as a stabilizer, emulsifier, thickener, suspending agent, bodying agent, and foam enhancer in foods (21 CFR 172.695). The regulation specifies that xanthan gum is purified by recovery with isopropyl alcohol (21 CFR 172.695(a)). In GRAS Notice No. 000121, a manufacturer determined that xanthan gum purified by recovery with an alternative solvent, ethyl alcohol, is GRAS for certain uses. In our letter responding to the GRAS notice (Ref. 23), we referred to the xanthan gum prepared by the alternative manufacturing process as "xanthan gum (ethanol precipitate)." We noted that the modified manufacturing process for xanthan gum (ethanol precipitate) does not comply with the specifications listed in 21 CFR 172.695; in order for xanthan gum (ethanol precipitate) to comply with 21 CFR 172.695, that food additive regulation would need to be amended to include purification of xanthan gum by recovery with ethyl alcohol. However, we had no questions about the manufacturer's determination that the specified uses of ethanol precipitate of xanthan gum are GRAS. The manufacturer was later informed by FDA that the common and usual name "xanthan gum" is permitted because xanthan gum (ethanol precipitate) is chemically indistinguishable from the food additive xanthan gum.

C. Tartaric Acid (21 CFR 184.1099 and GRAS Notice No. GRN 000187)

L (+) tartaric acid is affirmed as GRAS for use as a food ingredient (21 CFR 184.1099). The regulation specifies that tartaric acid is obtained as a by-product of wine manufacture (21 CFR 184.1099(a)). In GRAS Notice No. 000187, a manufacturer concluded that L (+) tartaric acid produced by an alternative manufacturing process (i.e., by the conversion of maleic anhydride to tartaric acid through the enzymatic action of the enzyme *cis*-epoxisuccinate hydrolase, contained in immobilized *Rhodococcus ruber* cells) is GRAS for the same use as described in 21 CFR 184.1099. In our letter responding to the GRAS notice (Ref. 24), we noted that the L (+) tartaric acid described in GRN 000187 substituted for the uses of tartaric acid prepared as described in 21 CFR 184.1099 and, thus, total daily intake of tartaric acid was not expected to change from the current level. We also noted that L (+) tartaric acid produced by the alternative method is chemically identical to the tartaric acid affirmed as GRAS in 21 CFR 184.1099 and meets the specifications for tartaric acid in the Food Chemical Codex (FCC), 5th ed., 2003. We had no questions about the manufacturer's determination that L (+) tartaric acid produced by the alternative manufacturing process is GRAS for the same use as described in 21 CFR 184.1099.

Appendix 2. Descriptions of the Principal Regulatory Submissions for Food Substances

A. Petition Process for Premarket Approval of a Food Additive

Our implementing regulation for the food additive petition process is in 21 CFR 171.1. In general, a food additive petition includes information such as:

- The name and pertinent information about the identity of the food additive (including chemical identity and composition; physical, chemical, and biological properties; and specifications prescribing the minimum content of the desired component(s) and identifying and limiting the reaction byproducts and other impurities) (21 CFR 171.1(c)A);
- Information about the manufacturing process and any person other than the petitioner who performs any manufacturing, processing, and packing operations for the additive (21 CFR 171.1(c)A and 21 CFR 171.1(j));
- The amount of the food additive proposed for use and the purposes for which it is proposed (21 CFR 171.1(c)B);
- Data establishing that the food additive will have the intended physical or other technical effect (21 CFR 171.1(c)C); and
- Full reports of investigations made with respect to the safety of the food additive (21 CFR 171.1(c)E).

If we find that the data and information submitted in a food additive petition establish that the food additive will be safe under the conditions of its intended use, we authorize the use of the food additive through a regulation (21 CFR 171.100). The regulation establishes the conditions under which the additive may be safely used (including specifications as to the particular food or classes of food in or on which such additive may be used, the maximum quantity which may be used or permitted to remain in or on such food, the manner in which the additive may be added to or used in or on such food), the function(s) for which the food additive may be added to or used and, as needed, any specific labeling requirements associated with the addition or use of the food additive. In establishing the regulation, we rely on the information in the food additive petition as well as other available data and information, and include memoranda documenting that review in the administrative record of the petition; however, the regulation reiterates or describes only a small fraction of the information in the administrative record of the petition.

In most cases, our regulations describe the identity of the food additive and the manufacturing process for the food additive. The degree of detail for these descriptions varies. As one example, the regulation for carrageenan (21 CFR 172.620) specifies that carrageenan is the refined hydrocolloid prepared by aqueous extraction from specifically named species of red seaweed. As another example, the regulation for xanthan gum (21 CFR 172.695) specifies that xanthan gum is a polysaccharide gum derived from *Xanthomonas campestris* by a pure-culture fermentation process and purified by recovery with isopropyl alcohol; the regulation for xanthan gum further specifies that xanthan gum contains D-glucose, D-mannose, and D-glucuronic acid as the dominant hexose units and is manufactured as the sodium, potassium, or calcium salt.

We have provided guidance to industry on administrative aspects of a food additive petition as well as on the preparation of data and information regarding the identity, manufacturing process, technical effect, and evaluation of safety of a food additive (Refs. 3, 6, 9, and 10).

B. Premarket Notification Program for a Food Contact Substance

Our implementing regulations for the premarket notification program for a FCS are in 21 CFR 170.100 through 21 CFR 170.106. In general, a notification for a FCS includes data and information analogous to those that would be submitted in a food additive petition (see section A in Appendix 2 of this document). However, some of the data and information that would be submitted in a premarket notification for a FCS are different in that they relate to the fact a FCS is not intended to be directly added to food; rather, it is the case that some amount of a FCS may migrate to food.

An FCN is effective only for the manufacturer, substance, and intended use identified in the notification. Any person wishing to rely on an FCN will need to determine that the FCS being marketed has been manufactured or supplied by the manufacturer identified in the FCN and is being used under the conditions that are the subject of the FCN.

We have provided guidance to industry on administrative aspects of a food contact notification as well as on the preparation of data and information regarding the identity, manufacturing process, technical effect, and evaluation of safety of a FCS (Refs. 5, 7, 10, and 11). Currently, we provide an Inventory of Effective Food Contact Substance Notifications on our Web site (Ref. 25). This inventory is not required by statute or regulation and should not be presumed to contain all information relevant to identity of the notified substance. In establishing a listing for a specific FCS in the Inventory of Effective Food Contact Substance Notifications, we use the information in the FCN; however, that listing reiterates or describes only a small fraction of the information in the FCN. By contrast the notification is required by statute to include all information relevant to the safety determination for the food contact substance.

C. "Threshold of Regulation" Program for a Substance Used in a Food Contact Article

Our implementing regulation for the Threshold of Regulation (TOR) process is in 21 CFR 170.39. Under 21 CFR 170.39, a substance used in a food-contact article (e.g., food packaging or food-processing equipment) that migrates, or that may be expected to migrate, into food will be exempted from regulation as a food additive because it becomes a component of food at levels that are below the threshold of regulation if the substance satisfies certain criteria relating to:

- Its potential carcinogenicity;
- The estimated dietary exposure to the substance;
- Its lack of technical effect in or on the food to which it migrates; and
- Its lack of significant adverse impact on the environment.

In general, a request for an exemption request under the TOR program includes information such as:

- Chemical composition;

- Detailed information on the conditions of use;
- Validated migration data;
- Information on either the amount of the food substance used in the manufacture of the food-contact article or on the residual level of the food substance in the food contact article; and
- An analysis of existing toxicological information on the food substance and its impurities.

We respond by letter to a person who requests an exemption under the TOR program. Currently, we maintain a list of exemptions under 21 CFR 170.39 on our Web site (Ref. 26).

D. Program to Notify FDA of a Determination That a Use of a Substance is Generally Recognized as Safe

Our implementing regulations regarding the criteria for eligibility for classification of the use of a substance as GRAS are in 21 CFR 170.30. Regulations identifying GRAS conditions of use for certain substances are in Part 182 and regulations affirming the GRAS status of the use of some food substances are in 21 CFR Parts 184 and 186, respectively. Importantly, the GRAS regulations do not apply to the use of a substance that meets the statutory definition of a color additive (see section II.B of this document).

In 1997, we proposed to establish a voluntary notification procedure whereby you may notify us of your determination that a particular use of a substance is GRAS (62 FR 18938; April 17, 1997). In 1998, we started accepting GRAS notices under the framework of the proposed rule (Ref. 8). In general, under that framework a GRAS notice includes information such as:

- The applicable conditions of use of the notified substance;
- Detailed information about the identity of the notified substance, including the method of manufacture and specifications for food-grade material;
- Information on any self-limiting levels of use; and
- A detailed summary of the basis for the notifier's determination that a particular use of the notified substance is not subject to the premarket approval requirements of the FD&C Act because such use is GRAS.

We evaluate whether each submitted notice provides a sufficient basis for a GRAS determination for the intended use and whether information in the notice or otherwise available to us raises issues that lead us to question whether the intended use of the substance is GRAS. Following this evaluation, we respond to the notifier by letter. Our letter summarizes the notifier's basis for determining that the intended use of the notified substance is GRAS, including information about the identity of, and manufacturing process for, the notified substance.

Currently, we provide a summary of information about GRAS notices in our GRAS Notice Inventory (Ref. 27). The GRAS Notice Inventory provides links to information such as the name of the substance, the name and address of the person who made the GRAS determination, and the letter we sent in response to the notice.

As is the case for a food additive, a GRAS regulation reiterates or describes only a small fraction of the information in a GRAS affirmation petition. Likewise, information in our response to a GRAS notice describing a notified substance reiterates or describes only a small fraction of the information in the GRAS notice.

E. Petition Process for Listing a Color Additive

Our implementing regulation for the color additive petition process is in 21 CFR 71.1. In general, a color additive petition includes information similar to that submitted in a food additive petition (see section A in Appendix 2 of this document).

If we find that the data and information submitted in a color additive petition establish that the color additive will be safe and suitable under the conditions of its intended use, we list the use of the color additive through a regulation (21 CFR 70.42(a)). The regulation may list the color additive for use generally in or on foods, or may prescribe the conditions under which the color additive may be safely used (including specifications as to the particular food or classes of food in or on which such color additive may be used; the maximum quantity of any straight color or diluent that may be used or permitted to remain in or on such food; and the manner in which such color additive may be added to or used in or on such food). In establishing the regulation, we rely on the information in the color additive petition as well as other available data and information, and include memoranda documenting that review in the administrative record of the petition; however, the regulation reiterates or describes only a small fraction of the information in the administrative record of the petition.

In most cases, our regulations describe the identity of the color additive and the manufacturing process for the color additive. The degree of detail for these descriptions varies. As examples:

- The regulation for astaxanthin (21 CFR 73.35) states the chemical name for astaxanthin and describes its color through its spectral properties (absorption maximum wavelength 484-493 nanometers in chloroform), but is silent on the manufacturing process.
- The regulation for dehydrated beets (beet powder) (21 CFR 73.40) describes the color of the additive as dark red powder and describes the manufacturing process as dehydrating sound, mature, good quality, edible beets
- The regulation for ultramarine blue (21 CFR 73.50) describes the color additive as a complex sodium aluminum sulfo-silicate (including an approximate chemical formula) that is a dark blue pigment. In describing the manufacturing process, the regulation specifies that ultramarine blue is obtained by calcining a mixture of kaolin, sulfur, sodium carbonate, and carbon at temperatures above 700 °C, and that sodium sulfate and silica may also be incorporated in the mixture in order to vary the shade.

We have provided guidance to industry on administrative aspects of a color additive petition as well as on the preparation of data and information regarding the identity, manufacturing process, technical effect, and evaluation of safety of a color additive (Refs. 4, 6, 9, and 10).