

The following three papers represent the personal opinions of individual personnel in Food and Drug Administration’s (FDA) Office of Food Additive Safety (OFAS), which is located within the Center for Food Safety and Applied Nutrition (CFSAN). As such, these papers do not represent official statements by FDA nor do they constitute an FDA guidance document. They are intended only as background information for The Pew Charitable Trusts Workshop on Enhancing FDA’s Evaluation of Scientific Data to Ensure Chemicals Added to Human Food Are Safe. These papers do not state any official FDA position and may not be relied upon as such.

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STATUTORY AND REGULATORY FRAMEWORK FOR FDA'S REVIEW OF DIRECT FOOD ADDITIVES, GRAS SUBSTANCES, AND FOOD-CONTACT SUBSTANCES¹

The purpose of this paper is to describe the statutory and regulatory provisions which govern FDA's premarket safety review of direct food additives, substances which are generally recognized as safe (GRAS) for addition to food, and food-contact substances.

THE FEDERAL FOOD, DRUG, AND COSMETIC ACT (the FD&C Act, 21 U.S.C. Section 340, et seq.)

The FD&C Act is the statute under which FDA regulates substances, which are intentionally added to food as ingredients or which are used in food processing or food packaging.

The 1958 Food Additives Amendment: In 1958, the FD&C Act was amended by adding Section 409 (21 U.S.C. § 348), which requires FDA authorization of food additives before they enter the market. Section 409 provides that a food additive is unsafe, and therefore may not be legally marketed or used unless the additive and its intended use are in conformity with a food additive regulation issued by FDA, or, in the case of a food additive which is a food contact substance (FCS), the additive and its intended use are in conformity with an effective food contact substance notification (FCN).²

The definition of "food additive" is central to how substances used in food or in contact with food are regulated by FDA. Section 201(s) of the FD&C Act (21 U.S.C. § 321 (s)) defines a "food additive" as any substance the intended use of which results or may reasonably be expected to result, directly or indirectly, in its becoming a component or otherwise affecting the characteristic of any food (including any substance intended for use in producing, manufacturing, packing, processing, preparing, treating, packaging, transporting, or holding food; and including any source of radiation intended for any such use); if such substance is not generally recognized as safe (GRAS)³ under the conditions of its intended use or is not subject to a sanction or approval issued prior to 1958 by FDA or the U.S. Department of Agriculture.^{4 5}

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² FCSs and FCNs are discussed in more detail subsequently in this paper.

³ GRAS substances also are discussed in more detail subsequently in this paper.

⁴ This is the portion of the definition which is pertinent to this paper.

⁵ A prior-sanctioned substance is the subject of a letter issued by FDA or USDA indicating no objection to a specific use. The prior sanction exists only for the specific substance under the specific conditions of use as set forth in a letter issued by FDA or USDA prior to September 6, 1958. Some, but not all, prior-sanctioned substances are codified in 21 CFR Part 181.

The 1960 Color Additive Amendments: The FD&C Act was amended in 1960 by the addition of Section 721 (21 U.S.C. § 379e) to require FDA authorization of color additives before they enter the market. Section 721 provides that a color additive is unsafe (and therefore subject to FDA enforcement action) unless the additive and its use are in conformity with a color additive regulation issued by FDA.

Section 201 (t) (21 U.S.C. § 321 (t)) of the statute defines a color additive as a “dye, pigment, or other substance” which, “when added or applied to a food, drug, or cosmetic, or to the human body or any part thereof, is capable (alone or through reaction with other substance) of imparting color” There is no exemption of GRAS substances in the definition of a color additive. Therefore, all color additives must be the subject of a regulation. Colorants for food packaging and other food-contact applications, however, are not regulated as color additives, but as food-contact substances. Colorants for food-contact applications are eligible for the GRAS exemption from the food additive definition.

REGULATION OF DIRECT FOOD ADDITIVES⁶ AND COLOR ADDITIVES

Regulations for food additives and color additives are issued by FDA in response to petitions. Any person (including government agencies) may file a food additive or color additive petition (and FDA may propose a regulation on its own initiative). *See* FD&C Act, Sections 409 and 721 and 21 C.F.R. Parts 71 and 171.

These same provisions of the statute and the regulations require that the petition and other information available to FDA establish that the food additive or color additive is safe for its intended use in order to support the issuance of a regulation permitting the use. FDA’s regulations provide the following safety standard for food additives (21 C.F.R. § 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. It is impossible in the present state of scientific knowledge to establish with complete certainty the absolute harmlessness of the use of any substance. Safety may be determined by scientific procedures or by general recognition of safety. In determining safety, the following factors shall be considered:

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

⁶ “Direct food additive” is not a term defined in the law or the regulations. It is used by FDA and others to identify food additives which are not food contact substances as defined in the FD&C Act, a definition which is discussed subsequently in this paper.

With respect to safety factors, FDA's food additive regulations state as follows (21 C.F.R. § 170.22):

“Except where evidence is submitted which justifies use of a different safety factor, a safety factor in applying animal experimentation data to man of 100 to 1 will be used; that is, a food additive for use by man will not be granted a tolerance that will exceed 1/100th of the maximum amount demonstrated to be without harm to experimental animals.”

It is important to note that, while the regulation establishes a default safety factor of 100 in extrapolating the results of studies in animals to assess risk to humans, it also preserves FDA's discretion to use different safety factors as warranted by the evidence in a particular case.

The same safety standard applies to color additives and to food contact substances.

In addition, food additives, color additives, and food contact substances are subject to the *Delaney* Clause (named after its Congressional sponsor), which states as follows (FD&C Act, Section 409 (c) (3) (A) (21 U.S.C. § 348 (c) (3) (A)):

“No additive shall be deemed to be safe if it is found to induce cancer when ingested by man or animal, or if it is found, after tests which are appropriate for the evaluation of the safety of food additives, to induce cancer in man or animal”

The *Delaney* Clause has been interpreted by FDA and by the courts as applying to the additive *per se*, not to constituents of the additive (e.g., starting materials or other impurities). Policy for Regulating Carcinogenic Chemicals in Food and Color Additives (the Constituents Policy), 47 Fed. Reg. 14464 (April 2, 1982); *Scott v. FDA*, 728 F.2d 322 (6th Cir. 1984). Constituents which show evidence of carcinogenicity are evaluated for safety through risk assessment rather than being subject to the absolute ban of the *Delaney* Clause.

The petitioner has the burden of demonstrating that the substance and its intended use meet the safety standard. The basic data requirements for petitions are identified in FDA's regulations (21 C.F.R. § 171.1 for food additives and § 71.1 for color additives). In addition, there are guidance documents with further information on the data requirements, and this guidance is available on FDA's website (www.fda.gov). FDA may require further data and information not specifically identified in the regulations or the guidance as necessary to determine safety.

The FD&C Act calls for FDA to act on food additive and color additive within 180 days of filing. Sections 409 (c) (2) and 721 (d) (1) (21 U.S.C. §§ 348 (c) (2) and 379e (d) (1)). Review of petitions sometimes extends beyond this period due to scientific complexity and the need for additional information.

FDA's regulations clearing specific direct food additives are found at 21 C.F.R. Parts 172 and 173 (for secondary direct additives, generally food processing aids). The color additive regulations are codified at 21 C.F.R. Parts 73 and 74.

REGULATION OF FOOD CONTACT SUBSTANCES

In 1997, the Food and Drug Administration Modernization Act (FDAMA) amended section 409 of the FD&C Act (21 U.S.C. § 348) to establish a premarket notification process as the primary method for authorizing new uses of food additives that are food contact substances (FCSs). A “food contact substance” is defined in section 409(h)(6) of the Act as “any substance intended for use as a component of materials used in manufacturing, packing, packaging, transporting, or holding food if such use is not intended to have any technical effect in such food.” Food contact substances often are used in food packaging, but the category includes components of food processing equipment and other substances used in processing food but which are not intended to have a technical effect in the food.

Prior to 1997, food contact substances which met the FD&C Act definition of “food additive” were regulated in the same way as direct food additives. Food contact substances were known as “indirect food additives.” Food additive regulations providing FDA authorization for the use of these substances were issued in response to food additive petitions. These regulations are codified at 21 C.F.R. Parts 175, 176, 177, and 178. The indirect food additive regulations remain valid.

However, with respect to food contact substances, the food additive petition process has been superseded by the food contact notification program. Food contact notifications (FCNs) are required for new uses of FCSs that meet the statutory definition of “food additive” (including new uses of FCSs that are covered by indirect food additive regulations for other uses). The FCN process is available, but not required, for FCSs that are not food additives (as a result of being GRAS, for example).

The FCN process differs from the food additive petition process in that the issuance of a regulation is not required for the FCS to be authorized by FDA for the intended use. Under the FD&C Act, an FCN becomes effective automatically, and the FCS is thereby authorized for use, 120 days after receipt by FDA of an FCN with all of the necessary information unless FDA determines within the 120-day period that the FCS has not been shown to be safe for its intended use and notifies the submitter of this determination. FD&C Act, Section 409(h) (2) (C) (A).

As discussed previously, the safety standard applied by FDA in evaluating an FCS is the same standard applied in the evaluation of food additives and color additives. The data and other information required in an FCN are identified in the regulations (21 C.F.R. § 170.101) and in guidance documents which are available on FDA’s website. As with respect to food additives and color additives, FDA may require whatever data are necessary to establish that the FCS is safe for the intended use. In addition, FDA has the discretion to require a food additive petition for an FCS under certain circumstances. 21 C.F.R. § 170.100 (c).

An FCN also differs from a food additive regulation in that it is effective only for the FCS manufactured or prepared by the manufacturer or supplier identified in the FCN submission. FD&C Act, Section 409 (h) (2) (C) (21 U.S.C. § 348 (h) (2) (C)); 21 C.F.R. § 170.100 (a).

Since no regulation is issued, FDA has chosen to maintain on its website an Inventory of Effective Food Contact Substance Notifications.

GENERALLY RECOGNIZED AS SAFE (GRAS) SUBSTANCES

As discussed above, substances which are generally recognized as safe (GRAS) under their intended conditions of use are excluded from the definition of “food additive” in Section 201 (s) of the FD&C Act. This means that authorization by FDA is not required in order for the substances to be used in the manner which has been determined to be GRAS. Any person may make their own GRAS determination without the need for FDA review or concurrence.

In 1997, FDA issued a proposed rule changing some of the regulations relating to GRAS determinations. 62 Fed. Reg. 18937 (April 17, 1997). One aspect of the proposal was to replace the process of issuing GRAS affirmation regulations in response to voluntary petitions with a notification procedure whereby any person may notify FDA of a determination that a particular use of a substance is GRAS. Although the proposed rule has not yet been finalized, FDA currently accepts such voluntary notifications. FDA does not reach a conclusion about the GRAS status of the intended use of a substance, but determines whether there are adequate data and other information to support the notifier’s GRAS determination. FDA responds with a letter indicating either that the agency has no questions about the determination or that the notice does not provide a sufficient basis for the GRAS determination. Before receiving such a letter, the notifier may withdraw the notification, which does not constitute an admission that the substance is not GRAS for the intended use.

In Section 201 (s), the FD&C Act provides two bases for a GRAS determination: (1) general recognition by qualified experts that the substance has been adequately shown through scientific procedures to be safe for the intended use; or (2) common use in food prior to 1958. As indicated above, “safety” in the GRAS context has the same meaning as for food additives and food contact substances – a reasonable certainty of no harm. Section 170.30 (b) of FDA’s regulations provides that general recognition of safety through scientific procedures requires the same quantity and quality of scientific evidence as is required to obtain approval of a substance as a food additive. GRAS substances are distinguished from food additives by the requirement of general recognition of safety, “which shall ordinarily be based upon published studies which may be corroborated by unpublished studies and other data and information.” 21 C.F.R. §170.30 (b).

Some GRAS substances are listed in FDA’s regulations at 21 C.F.R. Parts 182, 184, and 186. Section 182.1, however, explicitly states that “it is impracticable to list all substances that are generally recognized as safe for their intended use.” This statement recognizes that substances not listed by FDA as GRAS nevertheless may be determined to be GRAS by the private sector.

Additional detailed information on the FAP program, FCN program and GRAS program can be accessed from the Food Ingredients and Packaging section under the Foods topic of www.fda.gov.

DEVELOPMENT AND REVISION OF THE REDBOOK ⁷

REDBOOK ORIGINS

The development and publication of the 1982 Redbook (“Toxicological Principles for the Safety Assessment of Direct Food Additives and Color Additives Used in Food”) was in part an agency response to long-standing criticism that the agency’s regulatory criteria for evaluating the safety of food additives (21 C.F.R. § 170.20) and color additives (21 C.F.R. § 70.42) were too general and brief to provide meaningful guidance to the public. FDA developed safety testing guidance that more clearly described the Agency’s process of scientific decision making used in evaluating the safety of food additives and color additives. It was anticipated that this guidance would supply information useful to industry, our own agency reviewers and the general public.

In the 1982 Redbook a number of developments were listed; some were unique for that time. For example, a section, “Decision Elements,” described how to evaluate existing information on a substance and how to assess the need for additional studies to help assure the safe use of food additives and color additives. Moreover, determination of basic information required to assess the safety of these substances based on their molecular structures and the level of exposure of the human population to them was recommended. These two metrics were then used in a simple algorithm to define the type and extent of toxicity testing recommended. Standards for determining the rigor and quality of the study protocols were also provided. Furthermore, guidelines that suggested protocols for performance of the frequently used toxicological studies (tests) were discussed.

THE 1993 REVISION OF THE REDBOOK

By 1987, FDA was aware of the need for a revision of the 1982 Redbook. A steering committee composed of scientists from all of FDA’s product review offices and the Center for Food Safety and Applied Nutrition’s (CFSAN) toxicology laboratory research department joined together for this project. This effort included 50 scientists divided into 24 individual working groups and examined the scientific advances that had been achieved subsequent to the late 1970’s and early 1980’s. The Steering Committee’s recommendations for updates to the Redbook and those suggested by consumers, academic and industry scientists were carefully considered for integration into an updated version of the Redbook. This update effort was very labor- and resource-intensive. Multiple drafts of topic or chapter updates were developed and reviewed by the Steering Committee and the final modifications to the Redbook were reviewed and approved by senior scientific and management officials of the FDA.

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The new edition of the safety assessment guidance was referred to variously as Redbook II or the 1993 Redbook. It re-evaluated, updated and revised the study protocols used in the assessment of food additive and color additive safety, such as: 1) conventional feeding studies of all designs and durations; 2) carcinogenicity studies as well as *in vitro* genotoxicity studies; 3) reproductive and developmental studies; 4) expanded discussions and guidance in the study areas of metabolism and pharmacokinetics, immunotoxicology, neurobehavioral toxicology, unique and specialized additives, alternatives to whole animal testing, pathology and statistical assessment, human testing, and epidemiological study designs.

An “Emerging Issues” chapter was added to the 1993 version. This chapter discusses developing areas of scientific study; e.g., macro-additives, food ingredients derived from biotechnology processes, microbially-derived food ingredients, heritable and somatic genetic toxicity and advances in the development of alternative study designs (*in vitro* and *ex vivo*).

Sections of the 1982 Redbook were re-written to make them more user-friendly and clear by the addition of more introductory and explanatory discussions. All of these changes were proposed, reviewed, revised, and assessed by upper levels of the FDA and relevant scientists in the Department of Health and Human Services. In addition the scientists in academia, industry and from other agencies were made aware of the impending changes in the new Redbook and were invited to critique this version. As some of the changes proposed were departures from earlier protocol design recommendations, a public meeting was held to allow stakeholders to comment. Both editorial changes and substantive modifications to study design were addressed and, where appropriate, changes were incorporated. The draft version of Redbook II became publicly available in 1993.

REDBOOK 2000 AND BEYOND

A most important change in the public availability of the Redbook occurred in 2000 when it became available on the FDA/CFSAN internet website. In addition the title of the Redbook was changed to: “Toxicological Principles for the Safety Assessment of Food Ingredients.” This title change was meant to clarify that these toxicological principles, protocols and policies could be used for a broad range of regulated areas of substances added to or present in food; not just substances which meet the legal definitions of food additives and color additives. Thus, for example, the protocol guidance offered in the Redbook could be useful in determinations and review of generally recognized as safe (GRAS) status and in safety assessments of other regulated product categories when their toxicity or safety assessment are amenable to the types of studies discussed in the Redbook.

FDA decided to make future modifications to the Redbook available via the Internet when possible. The date of the last revision of each chapter is noted on the Internet.

The most important changes to the 1993 Redbook topics were incorporated in these areas: 1) how to expedite agency review of safety study data; 2) updates to the pathology and statistics review processes, and *in vitro* and *in vivo* genotoxicity study protocols; 3) comparison of various

feeding study protocols, including carcinogenicity, reproductive, developmental and neurotoxicity protocols. The chapter dealing with epidemiological studies was reviewed and updated.

PROCEDURES FOR REVIEW AND REVISION OF THE REDBOOK

This section of the paper is meant to provide an outline of the steps involved in the development, review, revision, outside critique and approval of further Redbook updates. The *development* of updates and new topics follows a progression of: presentation of new scientific study and techniques in literature or professional meetings, internal FDA review of the new study techniques and principles, and evaluation of applicability to supporting the safe use of food ingredients. Changes in the Redbook typically follow FDA's review of new study methodologies in connection with premarket submissions and post-market safety review. Among many questions and considerations are: 1) what new data or information are produced, 2) how mature and accepted are the study techniques, 3) how are the techniques being used in other regulatory science settings, 4) are the techniques recognized by international authoritative bodies as being appropriate for use, 5) have the techniques been adopted and/or validated by other federal agencies with regulatory authority over the safety assessment of consumer products or by international scientific and regulatory authorities (such as the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) and its international counterparts and the Organisation for Economic Cooperation and Development (OECD), and 6) can the new techniques be performed in a reasonably efficient manner to provide practical support for regulatory decisions on the safety of substances for addition to food?

After being successfully qualified in the essential characteristics outlined above, a new study technique enters the review for addition to the Redbook guidance. Further literature research and discussion with scientific experts within and outside of the confines of the FDA are held. When general scientific consensus develops regarding the purpose and reproducibility of the study method, investigation and discussion ensue as to whether this method is worthwhile for inclusion in updated guidance in the Redbook. A new scientific study method is included in guidance when it is clear that it has established a record of stability, reproducibility and reliability of data interpretation. Once a study protocol has proven itself, then the process discussed earlier for revision of the FDA Redbook is entered and engaged.

The next section of this paper, "Good Guidance Practices", discusses the FDA policies that apply agency-wide to the development and issuance of guidance such as the Redbook on how to supply data or information for various regulatory purposes.

GOOD GUIDANCE PRACTICES

Good guidance practices (GGP's) are FDA's policies and procedures for developing, issuing, and using guidance documents. GGPs apply to all FDA regulated products. GGPs provide

transparency and consistency in policy development. GGPs provide for equal public access and broad public participation in developing agency guidance. The public may review agency's guidance agenda and the public may submit suggestions to update guidance documents or suggest the need for new guidance documents. The public may provide drafts of such documents.

On September 19, 2000, FDA published a final rule on Good Guidance Practices (65 FR 56468). A new regulation was established to make the agency's procedures for development, issuance, and use of guidance documents clear to the public (21 CFR 10.115). The range of topics to which GGPs apply is quite broad. For example, guidance documents include, but are not limited to, documents that relate to: the design, production, labeling, promotion, manufacturing, and testing of regulated products; the processing, content, and evaluation or approval of submissions; and inspection and enforcement policies.

It is important to note that FDA's good guidance regulation explicitly confirms that the public has the right to provide input at any time on guidance documents which are being developed by the Agency. 21 CFR 10.115 (f) (1). In addition, the regulation states that the public can suggest areas for guidance document development. 21 CFR 10.115 (f) (2). Furthermore, the public has the right to submit drafts of proposed guidance documents for FDA to consider. 21 CFR 10.115 (f) (3).

With respect to GGPs there are special meanings to certain terms and these terms provide an explanation of which of two levels of guidance (Level 1 or Level 2) the agency will use to inform stakeholders of newly proposed changes in the manner in which FDA will do business.

"Level 1 guidance documents" include guidance documents that:

- 1) Set forth initial interpretations of statutory or regulatory requirements;
- 2) Set forth changes in interpretation or policy which are of more than a minor nature;
- 3) Include complex scientific issues; or
- 4) Cover highly controversial issues.

"Level 2 guidance documents" include guidance documents that:

- 1) Set forth existing practices or minor changes in interpretation or policy.

Level 2 guidance documents include all guidance documents that are not classified as Level 1. They are not required to be issued initially as a draft. The clearance process is less extensive. Therefore, in recognition of the burden of issuing Level 1 guidance as opposed to Level 2 guidance, more updates to the Redbook which qualify as Level 2 guidance have been issued by FDA.

Steps or procedures that are followed during the development of Level 1 guidance documents:

(i) Before FDA prepares a draft of a Level 1 guidance document, FDA can seek or accept early input from individuals or groups outside the agency. For example, FDA can do this by participating in or holding public meetings and workshops.

- (ii) After FDA prepares a draft of a Level 1 guidance document, FDA will:
 - (A) Publish a notice in the Federal Register announcing that the draft guidance document is available;
 - (B) Post the draft guidance document on the Internet and make it available in hard copy; and
 - (C) Invite public comment on the draft guidance document.
- (iii) After FDA prepares a draft of a Level 1 guidance document, FDA also can:
 - (A) Hold public meetings or workshops; or
 - (B) Present the draft guidance document to an advisory committee for review.
- (iv) After providing an opportunity for public comment on a Level 1 guidance document, FDA will:
 - (A) Review any comments received and prepare the final version of the guidance document that incorporates suggested changes, when appropriate;
 - (B) Publish a notice in the Federal Register announcing that the guidance document is available;
 - (C) Post the guidance document on the Internet and make it available in hard copy; and
 - (D) Implement the guidance document.
- (v) After providing an opportunity for comment, FDA may decide that it should issue another draft of the guidance document. In this case, FDA will repeat the steps to invite and consider public input.

FDA SAFETY ASSESSMENT OF DIRECT FOOD ADDITIVES, GENERALLY RECOGNIZED AS SAFE (GRAS) SUBSTANCES, AND FOOD CONTACT SUBSTANCES⁸

FDA's safety assessment of all types of substances added, directly or indirectly, to food follows well established steps of a typical risk assessment process: hazard identification, exposure assessment, dose-response assessment (also known as hazard characterization) and risk characterization.⁹

In this procedure, hazard identification is performed by using all relevant studies available, including those published in the scientific literature, those within Agency files, as well as those submitted by a petitioner. Studies and information reviewed by FDA for pre- and post-market safety assessments include computational toxicology studies (e.g., quantitative structure-activity relationship studies (QSAR)), *in vitro* studies, *in vivo* animal studies, and, less frequently, human clinical studies and epidemiological studies.

When FDA performs a safety assessment of a substance added to food, the Agency's scientists consider all of the relevant data submitted to the agency and any data found through their searches of the literature (e.g., PubMed) or available through other regulatory agencies (e.g., the European Food Safety Authority (EFSA)). Submitters are in fact required to assemble and address all relevant safety data available for any requested authorization. Studies recommended by FDA's guidance, as in the Redbook and the guidance with respect to food contact substance notifications¹⁰, are based on many years of scientific review by FDA of food additive petitions, food contact substance notifications, GRAS notices, and other submissions. In addition, FDA's guidance reflects the experience of other U.S. government regulators, international regulators and other experts.

Experiments sponsored by those who submit requests for FDA authorization generally are conducted according to internationally accepted and validated guidelines for a given experimental endpoint and usually employ Good Laboratory Practices (GLP) and quality assurance (QA) measures. The use of widely-accepted protocols allows regulators to have

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⁹ The outline of this process is described in "Risk Assessment in the Federal Government: Managing the Process," (National Research Council, 1983). Under the Delaney Clauses of the Federal Food, Drug, and Cosmetic Act, described in more detail below, carcinogens are categorically banned from being food additives or color additives as defined in the Act, and are not subject to the general risk assessment process.

¹⁰ Redbook,

www.fda.gov/Food/GuidanceComplianceRegulatoryInformation/GuidanceDocuments/FoodIngredientsandPackaging/Redbook/default.htm; Food Contact Substance Toxicology Guidance, www.fda.gov/Food/GuidanceComplianceRegulatoryInformation/GuidanceDocuments/FoodIngredientsandPackaging/ucm081825.htm.

confidence in the results of the observed findings, negative and positive, and the use of GLP and QA affords confidence in the validity of the information submitted to the Agency¹¹.

In performing the safety assessment, FDA reviewers must critically evaluate the studies submitted or otherwise obtained regardless of the source of the information. Certain factors, which have been identified over time, are essential to consider in determining the weight accorded to each toxicity study used in making a safety decision. These factors include the following:

1. Route of administration (ingestion, injection, etc.);
2. Sample size and statistical analysis;
3. Toxicity endpoint measured;
4. Plausibility of results;
5. Dose response;
6. Result differences by sex;
7. Repeatability;
8. Potential environmental contamination of samples.

These factors vary in significance, depending on the nature of the study; however, all studies must be appropriately designed and conducted

FDA considers that human exposure to ingredients in food is chronic over a lifetime. FDA is often most interested in studies that mimic this human exposure scenario. However, chronic studies may not be necessary depending on the chemical nature of the substance being tested and the estimate of human exposure (i.e., relatively innocuous substances used at low levels). Together, exposure as it relates to intended use, along with structural alerts and the results of relevant toxicity tests, define the breadth of data required for a given safety assessment. Most data needs are determined on a case-by-case basis.

Ordinarily, the test article used in toxicity testing would be the article of commerce. Although toxicity testing on the substance of interest is most relevant, testing on chemically or biologically similar compounds can also be used in the safety assessment. For all types of toxicity experiments, it is critical for the investigators to accurately characterize the material being tested and to make the results of the characterization available to the Agency. This will help FDA determine the relevance of the test results to the safety assessment for the substance of interest.

FDA's toxicological guidance serves as a starting point for determining an appropriate testing strategy for establishing the safety of an ingredient to be added to food. During the course of an assessment, safety questions may arise that cannot be addressed without additional data or data may be available that mitigate the need for certain tests. The process of review itself is determinative as to whether the data set is adequate and whether reasonably anticipated hazards

¹¹ For studies which are not conducted under GLP, FDA's regulations on food contact substance notifications (FCNs) permit the agency to require third party validation of the data. The primary reason for this regulation is to assure that FDA has the tools needed to meet the 120-day deadline for reviewing FCNs. The request for third-party validation is discretionary with FDA, and the Agency exercises this discretion only in cases where the additional information is important to the determination of safety.

are adequately addressed. As a result, the review process is typically iterative and involves ongoing interactions with the sponsor of a submission. This leads to multiple cycles of data requests, clarifications, and analyses that may result in more or less testing than is typically recommended. FDA provides testing recommendations; however, it does not have a prescriptive list of tests required in each and every case. This allows for alternative testing strategies and approaches to be incorporated into the safety assessment for various ingredients added to food.

The hazard identification for a substance is performed by toxicologists with the assistance of pathologists, statisticians, epidemiologists, and other specialists where needed. From all studies, the toxic hazard most relevant to protect human health is identified. The safety assessment and risk management decisions require comparison of the potential human exposure with the dose that was administered in the toxicology testing.

The dose response portion of any safety assessment typically involves identification of the most conservative no observed adverse effect level (NOAEL) or benchmark dosing level (BMDL) in the most robust studies as determined based on the factors identified above. The adverse effect levels determined from the testing in animals then are used to derive safe levels of human exposure. In cases where consumer exposure is very low, and no specific potential harm is identified in testing or through other analysis (e.g., structure activity analysis), the safety assessment may be based on genetic toxicity data and other data and information which do not involve a dose response relationship.

The default safety margins between actual human exposure and predicted toxicity from animal testing usually have been on the order of 10 to 100 to 1000 or 2000, depending on the robustness of the safety data and whether human toxicological information is available. FDA's regulations call for a safety margin of 100 in applying animal testing data to estimate human risk (21 C.F.R. § 170.22), but FDA may use other safety margins in accordance with the data in specific cases.

Exposure assessment typically uses conservative assumptions regarding the use level of a direct additive or conservative testing parameters regarding likely migration into food from food contact materials. Data utilized for the exposure assessment typically include the proposed maximum use level of a substance, analytical data on the level of the substance in food, analysis of food consumption surveys, or analysis of the amount of potential migrants from food contact materials. The result of this exposure determination is usually referred to as the Estimated Daily Intake (EDI). This step in the process is critical for FDA to fulfill its legal mandate to determine the safety of the substance for its intended use in the food supply.

It is the intended use of the substance that properly defines the scope of FDA's inquiry into safety, and this is a critical factor for determining how the Agency reviewers apply data in the safety determination. To characterize risk the EDI is compared to the NOAEL or BMDL considering default margins of safety and any other relevant factors to ascertain the margin of safety between expected human exposure and the predicted level of no adverse biological effect from safety studies.

The risk assessment process for potentially carcinogenic food additives and color additives is different due to the Delaney Clauses in the Federal Food, Drug, and Cosmetic Act ("FD&C

Act”). The Delaney Clauses, named after their chief Congressional sponsor, provide that no substances which meet the statutory definitions of food additive or color additive “shall be deemed to be safe if it is found to induce cancer when ingested by man or animal, or if it is found, after tests which are appropriate for the safety of food additives [or color additives], to induce cancer in man or animal” FD&C Act, Section 409 (c) (3) (A), and Section 721 (b) (5) (B) (i); 21 U.S.C. §§ 348 (c) (3) (A) and 379e (b) (5) (B) (i). Therefore, carcinogens are automatically banned as food additives and color additives (as defined in the FD&C Act) without regard to a risk assessment. The Delaney Clause for a food or color additive applies to the additive itself, not to its constituents. Therefore, the constituents of an additive can be evaluated under the general safety standard using risk assessment. FDA’s has published its constituents’ policy in the Federal Register.¹²

In summary, FDA has a process to assess the safety of ingredients added to food that has developed over 50 years and that has been informed by review experience. The safety assessment considers what the ingredient is, how much is added to food, and whether the ingredient is safe for its intended use. Safety is based on a collection of scientific data and information that must withstand scientific, procedural, and legal challenges from all sides. The safety decision is a consensus decision based on a fair evaluation of all the data. FDA’s approach to safety assessment incorporates established principles of risk assessment. The tools for risk assessment have advanced over time although new approaches are still needed. The current approaches to assessing the safety of food ingredients are well-accepted both nationally and internationally by scientists qualified to determine the safety of substances directly or indirectly added to food. FDA’s safety evaluation process is flexible and able to accommodate new developments in science.

¹² Policy for Regulating Carcinogenic Chemicals in Food and Color Additives (the Constituents Policy), 47 Fed. Reg. 14464 (April 2, 1982); *Scott v. FDA*, 728 F.2d 322 (6th Cir. 1984)). To determine carcinogenicity, CFSAN has employed an internal Cancer Assessment Committee (“CAC”) of interdisciplinary experts since 1978. The CAC deliberations are designed to reach a scientific weight of the evidence consensus for whether or not a substance is a carcinogen.



Statutory and Regulatory Framework for FDA's Review of Food Additives, GRAS Substances, and Food Contact Substances

Presented by Antonia Mattia, Ph.D.
FDA/CFSAN/OFAS

The Pew Charitable Trust's Pre-Workshop Webinar
March 29, 2011

Presentation Outline

- Overview of **OFAS** food ingredient **responsibilities**.
- Statutory **framework** for FDA's review of food ingredients (i.e., food additives, GRAS substances, and food contact substances).
- Redbook: FDA's **guidance** on toxicological principles for the safety assessment of food ingredients.
- **Risk assessment** to support regulatory decisions.

Office of Food Additive Safety



OFAS is responsible for the safety of ingredients added to food. OFAS receives and reviews food additive petitions, GRAS notices, and notifications for food contact substances.



The Food “Ingredient” Universe

Direct Food Ingredients:

Sweeteners; preservatives; nutrients; fat substitutes; texturizers (e.g., thickeners, emulsifiers); flavors

Color Additives: In food, animal feed, drugs, cosmetics, and medical devices (e.g., sutures, contact lenses)

Food Irradiation Equipment:

To Process food or to inspect food

GRAS Substances: Enzymes; fibers; proteins; lipids; sugars; MSG; antimicrobials; phytosterols/stanols; flavors; infant formula ingredients

Food Contact Substances:

Coatings (paper, metal, etc.); new/recycled plastics including polymers and monomers; paper; adhesives; colorants, antimicrobials, and antioxidants in packaging; packaging materials used during food irradiation; packaging “formulations”

Processing Aids: Antimicrobials (meat and poultry processing); defoamers; ion exchange resins

Foods/Ingredients Produced

Via Biotechnology: Plants w/ herbicide resistance or insect resistance; delayed ripening, etc.

The Federal Food, Drug, and Cosmetic Act of 1938 (FD&C Act)



- 1958 Food Additives Amendment to the FD&C Act defined “food additive”.
 - Required pre-market approval of new uses of food additives.
 - Established the standard of safety, the standard of review, and formal rulemaking procedures for food additives.
 - GRAS substances are excluded from the definition of a food additive.
-
- In 1960, Color Additive Amendments required pre-market review for color additives.
 - FD&C Act was further amended in 1997 to establish a mandatory premarket notification process for food contact substances.

Statutory Definition of “Food Additive” (FD&C Act Section 201(s))

- “any substance, the intended use of which results or may be expected to result, directly or indirectly, in its becoming a component or otherwise affecting the characteristics of any food...”
- Potentially includes a very wide range of substances as food additives.

Statutory Definition of “Color Additive” (FD&C Act Section 201(t))

- A material which is a dye, pigment, or other substance ... and when added or applied to a food, drug, or cosmetic, or to the human body or any part thereof, is capable (alone or through reaction with other substance) of imparting color thereto;
 - Excludes substances determined by the Secretary to be used solely for a purpose other than coloring.
- A color additive is unsafe if not used in accord with a regulation/ exemption (21 CFR 721(a)).
- No GRAS exemption.



Premarket Approval Of Food Or Color Additives Occurs Via a Petition Process

- Safety-based approval (not risk:benefit analysis).
- Procedures -
 - Public notice of filing is given in the Federal Register.
 - A food or color additive is not approved until a regulation is published in the Federal Register, including a preamble laying out the rationale of the action.
- Regulations are “generic” (not a license): anyone who complies may add the additive to food.

Contents of a Food Additive Petition

- Identity and composition of the food ingredient.
- Manufacture and specifications.
- Use in food must consider -
 - Types of foods,
 - Levels in those foods, and
 - Intended effects.
- Estimated Daily Intake (EDI).
- Analytical methodology.
- Full reports of safety data, including toxicological and other studies – Acceptable Daily Intake (ADI).
- Proposed tolerances, if needed.
- Environmental information.

Food Ingredient Safety Assessment

- **What exactly is the food ingredient and how much is there in food?**
 - Identity and composition
 - Method of manufacture
 - Specifications
 - Use level and exposure
- **Is it safe for its intended use?**
 - ADME data and information
 - Preclinical or clinical studies as appropriate
 - Other special studies
- **Is other case-specific information needed?**

Chemistry Data and Information

Identity

- Chemical Name and CAS Number
- Structure and Molecular Weight
- Physical Characteristics

Manufacturing Process

- Full description of process
- List of chemicals/reagents used

Specifications

- Typically proposed by petitioner or reference published specs (FCC)
- Should include description of the additive, identification tests, purity assay, and limits for impurities/contaminants

Stability

- Data demonstrating the stability
- Discussion of the fate of the additive

Technical Effect and Use

- Type of food and use level
- Data to show that the use level accomplishes the technical effect

Analytical Methodology

- If a use limitation of the additive is required for safe use, the petition must include a method able to quantify the substance for the purpose of enforcing the limit

Assessment of Dietary Intake

- Estimate of dietary intake by consumers to the food additive (and by-products of concern) resulting from eating food(s) containing the additive.
- Petitioner provides an estimate, which OFAS confirms.
- Calculated as an estimated daily intake (EDI)
 - Assumes chronic or average daily intake over a lifetime, and
 - Is typically calculated for the mean and 90th percentile consumer.

Typical Toxicological Studies

- Short-term tests for **genetic toxicity** (in vivo and in vitro testing).
- **Metabolism** and **pharmacokinetic** studies.
- **Subchronic feeding studies** (at least 90 days) in a rodent (e.g., rat) and non-rodent (e.g., dog) species.
- Two-generation **reproduction** study with a teratology phase (developmental toxicity study) in a rodent (e.g., rat).
- **Chronic feeding studies** (at least one year) in a rodent (e.g., rat) and non-rodent (e.g., dog) species (may be conducted as a component of a lifetime carcinogenicity study in rodents).
- **Two-year carcinogenicity** studies in two rodent species (e.g., rats and mice). The rat carcinogenicity study should also include an *in utero* phase.
- Other studies as needed (e.g., **neurotoxicity** and **immunotoxicity**) based on available data and information about the substance.

THE SAFETY DECISION

- Must protect public health.
- A consensus decision based on a fair evaluation of all the available data.
- Made in the absence of complete knowledge.
- Decisions are time-dependent.
- Must withstand scientific, procedural, and legal challenge from all sides.

The Delaney Clause

- There is an anti-cancer clause in the FD&C Act.
- Food additives, color additives, and food contact substances are subject to the Delaney Clause.
- It states that..
 - “No additive shall be deemed to be safe if it is found to induce cancer when ingested by man or animal, or if it is found, after tests which are appropriate for the evaluation of the safety of food additives, to induce cancer in man or animal...”

Carcinogenic Risk Assessment

- Interpretation of the Delaney clause -
 - Applies to the additive itself, not the constituents of the additive.
 - Constituents of the additive can be evaluated under the general safety standard using risk assessment.

(Scott v. FDA, 728 F. 2d 322 (6th Cir. 1984))



Regulations Are Published in the Title 21 of the Code of Federal Regulations (CFR)

| Part(s) | Type of Food Ingredient |
|-------------------|---------------------------------|
| Parts 73 and 74 | Color Additives |
| Part 172 | Direct Food Additives |
| Part 173 | Secondary Direct Food Additives |
| Parts 182 and 184 | GRAS |
| Parts 175-178 | Indirect Food Additives |

THE “GRAS EXEMPTION”

FD&C Act Section 201(s)

- Anything added to food is a food additive unless it is ***generally recognized as safe*** (GRAS).
- A substance is GRAS if –
 - It is generally recognized,
 - By qualified experts,
 - As safe through scientific procedures*,
 - For its intended use.

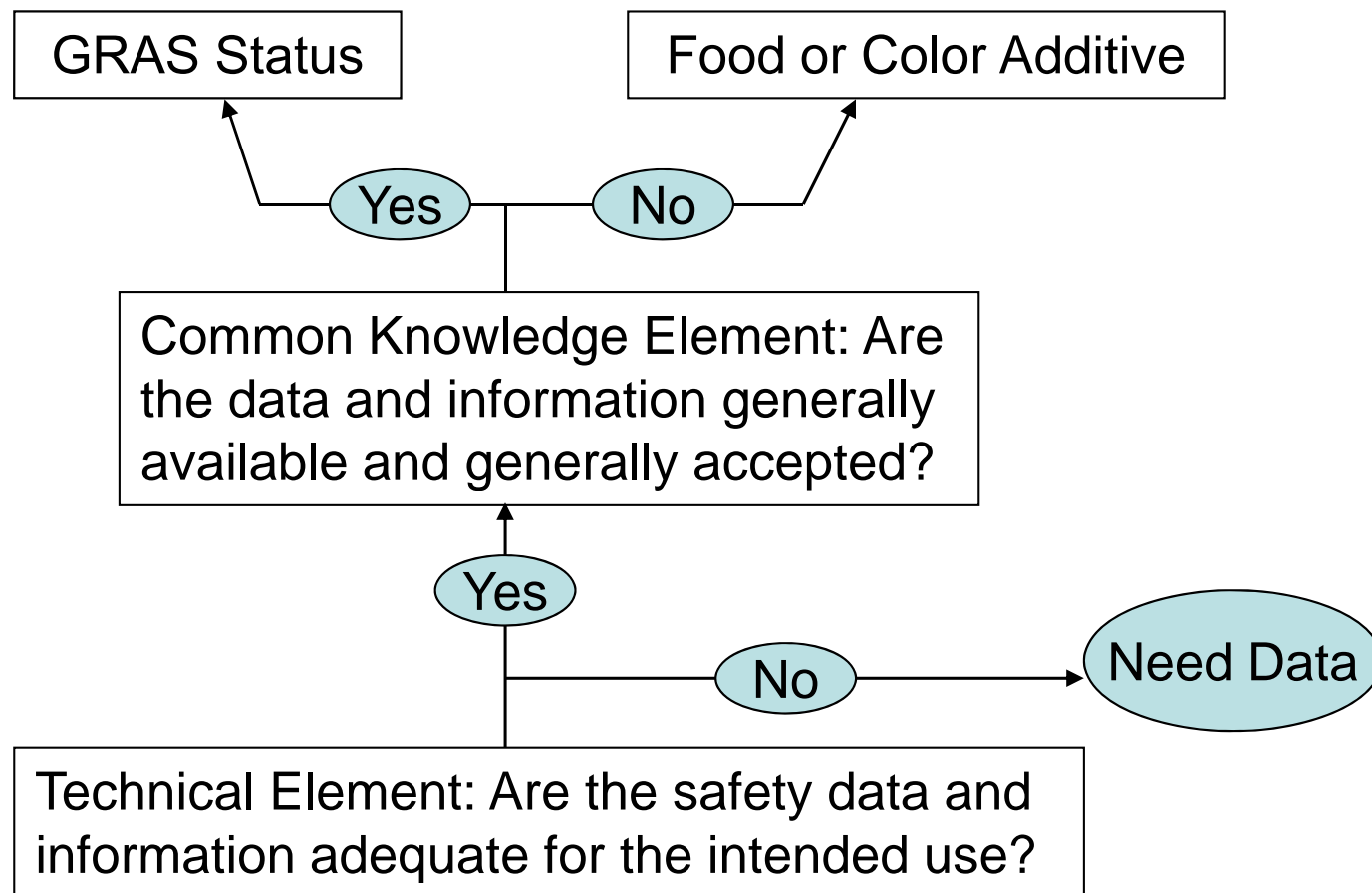


*or, in the case of a substance used in food prior to January 1, 1958, through either scientific procedures or experience based on common use.

Why Have A GRAS Exemption In the 1958 Food Additive Amendments?

- Substances “generally recognized as safe” (GRAS) were exempted from the broad definition of “food additive.”
- Consequently, there is no mandatory pre-market review for GRAS substances.
- This currently permits FDA to -
 - Exercise reasonable scientific judgment in ensuring safety, and
 - Expend resources commiserate with the risk to public health.
- There was a historical reason, too, which was not to disrupt the food supply at a time when there were no food additive regulations.

Common Knowledge: Distinguishes GRAS Substances from Food Additives



Direct Versus Indirect Additives

*“...any substance the intended use of which results or may reasonably be expected to result, **directly or indirectly**, in its becoming a component or otherwise affecting the characteristics of any food...”*

- **Direct Additives**

Substances that are added directly to a food for a technical purpose.

- **Indirect Additives**

Substances that become a part of the food due to its packaging, storage or handling.

Food and Drug Administration Modernization Act (FDAMA) of 1997

- Established a premarket notification process for authorizing new uses of food contact substances
- Provided a definition...
 - “[A]ny substance intended for use as a component of materials used in the manufacturing, packing, packaging, transporting, or holding food if such use is not intended to have any technical effect in such food.”
- Components of food processing equipment and other substances used in processing food are included.
- Indirect food additives are now “food contact substances.”

Food Contact Substances: New Statutory Language

- A food contact substance is deemed safe under § 409(h) if:
 - Firm notifies FDA of the proposed use 120 days in advance of marketing, and
 - FDA does not notify the firm within that period that the proposed use is unsafe.

Food Contact Notification Process

- Notifications are effective 120 days after the date of receipt, and the food contact substance may be marketed, **unless** FDA objects to the notification.
- Information in a notification is not disclosed unless and until the notification becomes effective.
- Notification is in effect **only** for the notified substance and for the notifier.

Food Contact Substances: Options

- Food contact substances can be regulated by processes other than the Food Contact Notification Program if -
 - Exposure to the FCS is > 1 ppm (FAP), or
 - Exposure to the FCS is < 0.5 ppb or $< 1\%$ of ADI for regulated direct additive (Threshold of Regulation), or
 - More than 120 day review period is necessary due to complexity or safety concerns (convert to food additive petition).

Safety and Review Standards

- Standard of safety
 - Reasonable certainty of no harm
- Standard of review
 - Fair evaluation of all of the data

These standards are the same for food and color additives, GRAS substances, and food contact substances.

REASONABLE CERTAINTY OF NO HARM (Legislative History of the FD&C Act)

“The concept of safety used in this legislation involves the question of whether a substance is hazardous to the health of man or animal. Safety requires proof of a reasonable certainty that no harm will result from the proposed use of an additive.”

“It does not -- and cannot -- require proof beyond any possible doubt that no harm will result under any conceivable circumstance.”

(H.R. Report No. 2284, 85th Congress, 1958.)

Harm Is Not Defined in the FD&C Act

- Although the concept of “harm” is central to the act’s safety standard, neither the statute, nor regulations implementing the food additive provisions, define harm.
- However, Congressional intent is clear from the legislative history of the 1958 amendment.
- The legislative history reflects that an effect is harmful if it affects health, not if it is simply an undesirable or unexpected effect that has no adverse health consequences.

Roles and Responsibilities

- The **petitioner or notifier** has the burden to demonstrate a “***reasonable certainty of no harm***” from the intended use of the ingredient.
- This requires that the **FDA** assess whether it has received adequately documented answers to appropriate questions of probative value.

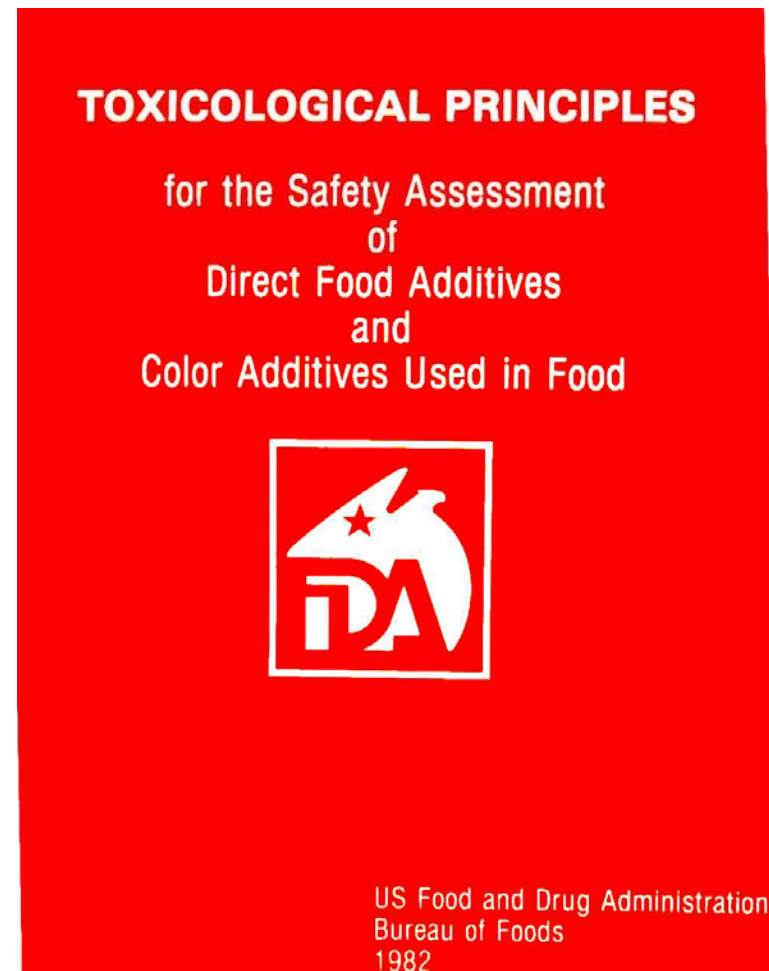


Comparison of the regulatory approaches for various food ingredients.

| Petition Process | GRAS Notification | FCS Notification |
|--|--|---|
| For food additives since 1958 and for color additives since 1960 | 1997 to now (previously a GRAS affirmation petition process) | Since 1997 (previously handled as “indirect” food additive petitions) |
| Mandatory | Voluntary | Mandatory |
| Industry submits a petition asking FDA to issue a regulation | Notifier informs FDA of their view that a use of a substance is GRAS | Industry submits a notification |
| FDA owns the safety decision | Notifier owns the safety decision; FDA evaluates the notifier’s basis | FDA owns the safety decision but there is a 120-day “hammer” |
| FDA publishes a regulation | FDA responds by letter (no questions, no basis, withdrawal) | FDA responds by letter (deficiency, effective, objection) |
| Petition is available publicly through FOIA | FDA responses, and more recently entire GRAS notices, are published on FDA’s website | FDA maintains a database of effective notifications on its website |

FDA/CFSAN Published The Redbook in 1982

- The Redbook provided guidelines to assist petitioners (and later notifiers) in developing and submitting information to FDA.



The 1982 Redbook

- Criteria for evaluating the safety of food and color additives are in 21 CFR 70.42 and 170.20, respectively.
- These were considered too general to provide meaningful guidance to the public.
- The Redbook set out to -
 - Describe how existing information is considered and how the need for additional studies is assessed, and
 - Provide rigorous protocols for commonly used toxicology studies.

Updates and New Topics in Redbook

- New data appears from literature and reviews of submissions.
- FDA reviews and evaluates its applicability to safety assessment.
- Considerations are many –
 - Is the new scientific study or technique widely accepted? Is it being used in regulatory settings?
 - Is it recognized by other authoritative bodies?
 - Are data acquired in a reasonably efficient manner?
- FDA engages with scientific experts as needed.
- Are data from the new study or technique reproducible and reliably interpreted? If so, consider a Redbook revision.

The 1993 Redbook or Redbook II

- The first revision, guided by an FDA Steering Committee, was resource-intensive.
- Recommendations from consumers, academic and industry scientists were considered.
- FDA held a public meeting to vet the changes.
- Conventional study protocols were updated.
- Discussion to reflect new advances in science and emerging issues was added to this revision.

The Redbook 2000

- New title: *Toxicological Principles for the Safety Assessment of Food Ingredients*.
- Available on the FDA/CFSAN website.
- Revisions are noted with a publication date at the end of individual chapters.

Updates to the Redbook are Guidance

- FDA has policies and procedures that must be followed in developing, issuing, and using guidance documents, such as Redbook (i.e., Good Guidance Practices).
- This is to –
 - Ensure that guidance practices are transparent, consistent and accountable, and
 - Encourage public participation in guidance development.
- Guidance can be Level 1 or Level 2.
 - Level 1 – Initial interpretation of statutory or regulatory requirements, policy changes, complex scientific issues, controversial issues.
 - Level 2 – Existing practices or minor changes in interpretation or policy.

Good Guidance Practices (GGPs)

- For Level 1 guidance, FDA gets outside input -
 - FDA announces draft guidance in a FR notice,
 - FDA posts guidance on the web/provides hard copy; and,
 - FDA invites public comment.
- FDA reviews comments and incorporates suggested changes as appropriate; then, FDA announces the guidance again in a FR notice, makes the guidance available, and implements it.
- Alternative approaches to guidance recommendations are acceptable – if compliant with relevant statutes and regulations.
- Most changes to the Redbook have been Level 2 guidance.

Other Guidance and Guidelines

- EPA - <http://www.epa.gov/>
- EFSA - <http://www.efsa.europa.eu/>
- FSANZ - <http://www.foodstandards.gov.au/>
- JECFA - <http://www.who.int/ipcs/food/jecfa/en/>
- OECD - <http://ntp-apps.niehs.nih.gov/iccvampb/OECD.cfm>
- Health Canada - <http://www.hc-sc.gc.ca/index-eng.php>

This is certainly not an all inclusive list; there are many other valuable documents relevant to food ingredient safety used by FDA scientists and technical reviewers.

Risk Analysis

- Describes three components of the risk assessment process.
- Components are separate but interactive.
- Orderly evaluations and science-based decisions about food ingredients are facilitated.



Risk Assessment

- Risk assessment is a scientifically based process consisting of the following steps -
 1. Hazard identification,
 2. Hazard characterization (includes dose-response),
 3. Exposure assessment, and
 4. Risk characterization.
- Includes quantitative risk assessment, and also qualitative expressions of risk, as well as an indication of the uncertainties.

Food Safety Assessment

- Acceptable Daily Intake (ADI)
 - Toxicology
 - Animal studies
 - Uncertainty factors
- Estimated Daily Intake (EDI)
 - Amount added to food
 - Amount of food consumed
- Safe if the EDI does not exceed the ADI, i.e., $EDI/ADI < 1$

Safety and Uncertainty

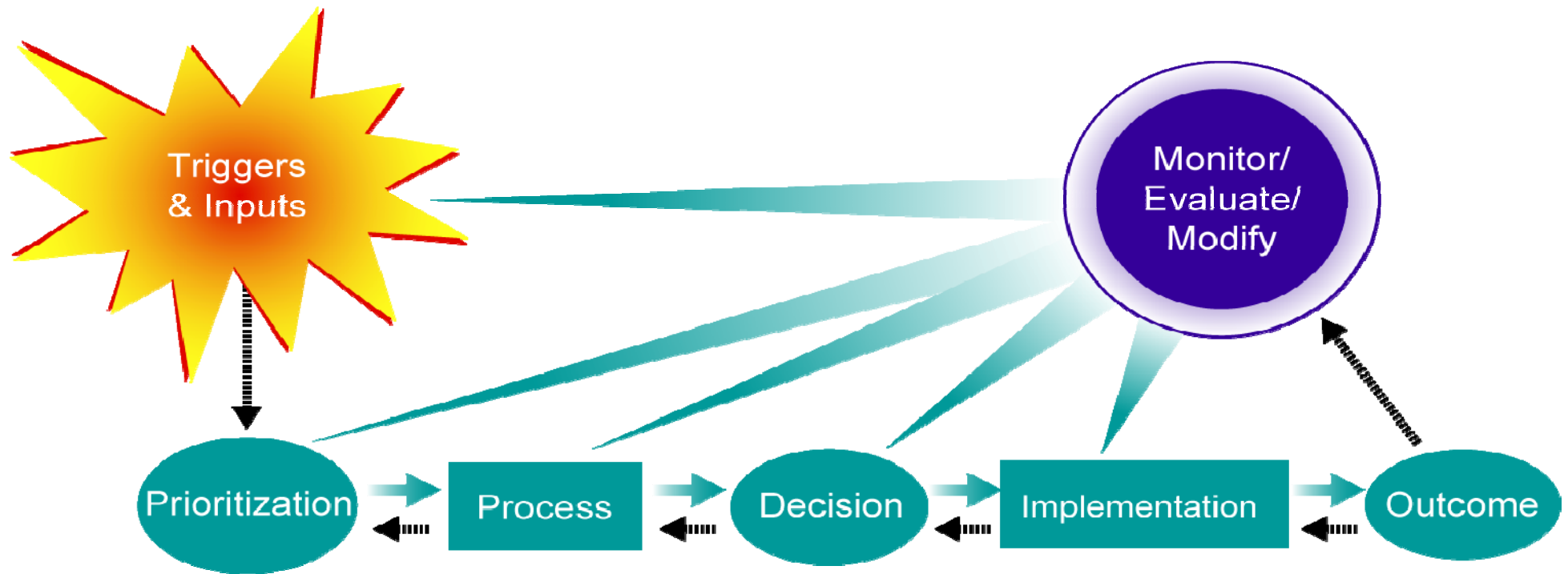
- Decisions must be made in the face of uncertainty
- The uncertainty cannot be out-of-line with what has been previously tolerated in the context of all previous similar safety decisions



CFSAN's Risk Management Framework

- Risk analysis includes risk management.
 - Process of weighing policy alternatives and implementing appropriate control options, including regulatory measures.
- CFSAN's risk management framework addresses –
 - How projects are identified, prioritized and completed; and,
 - How the outcomes of decisions are monitored and re-evaluated.

CFSAN's Risk Management Framework



Summary and Conclusions

- OFAS handles a variety of food ingredients.
- The universe of food ingredients is governed by statutory requirements related to safety.
- Redbook and a host of other documents provide guidance.
- Safety assessment is risk assessment.
- Decisions must protect public health and withstand challenges.

Comments and Questions ???

