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FDA'S food ingredient approval process[☆] Safety assurance based on scientific assessment

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ABSTRACT

Fifty years ago, the Food and Drug Administration (FDA) began implementing new provisions of the Federal Food, Drug, and Cosmetic Act aimed at assuring the safety of new food additives before they enter the marketplace. Today, the agency's procedures for premarket evaluation of food additive safety have evolved into a scientifically rigorous, sound and dependable system whose objective and independent evaluations by FDA scientists assure that new food additives are safe for their intended uses before they arrive on the consumer's plate. Although controversy often surrounds food additives in the popular media and culture, and science-based challenges to FDA's decisions do arise, the agency's original safety judgments successfully withstand these challenges time and again. This article reviews the basic components of the FDA's decision-making process for evaluating the safety of new food additives, and identifies characteristics of this process that are central to assuring that FDA's decisions are marked by scientific rigor and high integrity, and can continue to be relied on by consumers.

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1. Introduction

In the United States a range of government agencies have responsibility to ensure the safety and security of goods that American consumers purchase in the marketplace. Administering these responsibilities often requires specialized knowledge and the evaluation of information well beyond the scope or depth of an ordinary citizen's capabilities or interest. Typical consumers of food products certainly do not have the time or capacity to evaluate biochemical and safety data on every substance they encounter, or to assess for themselves on a daily basis the chemical components of every product they might consider purchasing. In the case of food, Congress has entrusted the Food and Drug Administration (FDA) with the responsibility to oversee the safety of food ingredients, including the premarket safety evaluation of new food additives destined for our foods. In this way consumers are freed from having to make their own personal judgments on a product-by-product basis about

food ingredient safety issues each time they wish to make a purchase. Consumers, of course, still make personal decisions about the products they select based on information provided on the food label and their own preferences, but they do not have to review the laboratory data from the animal feeding studies and other safety studies just to decide whether to purchase a food item in the supermarket. This paper outlines major features of the system currently used by the FDA in performing its food additive safety evaluation responsibilities on behalf of the American consumer. This system began *de novo* in 1958 when Congress passed, and President Eisenhower signed into law, the Food Additives Amendment to the Federal Food, Drug, and Cosmetic Act (FD&C Act, or the Act).^{3,4}

³ The Food Additives Amendment of 1958 to the Federal Food, Drug, and Cosmetic Act, Pub. L. 85-929, 72 Stat. 1784 (codified as amended in 21 U.S.C. 348). Two years later, in 1960, Congress passed the Color Additive Amendments to the Act which established a similar regulatory regime for color additives. In the context of food, both food additives and color additives are often dealt with together because many of the statutory and regulatory requirements are similar, despite the fact that they are defined separately in the FD & C Act (Section 201(s) for food additives and Section 201(t) for color additives, respectively) and color additives are explicitly excluded from the food additive definition, along with pesticides, prior sanctioned food ingredients, dietary supplements and new animal drugs. Although many of the statutory and regulatory standards and procedures for food additives apply as well to color additives, there are some notable differences between these two classes of regulated entities. For example, the effective date of color additive regulations and the post-approval regulatory procedures differ somewhat from those for food additives. Color additives may be used not only in foods, but also in cosmetics, drugs and medical devices. Therefore, although we often refer in this paper to

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2. Food ingredient ABC's

Throughout history, there are innumerable references to the use of food ingredients (such as salt, seasonings and a host of other substances added to food that perform important technical functions in food) as well as techniques (such as culturing and fermentation) used in the preservation and processing of foods. During the mid-20th Century, however, and prior to the passage of the 1958 Food Additives Amendment, the United States was still largely an agrarian society where food was often locally grown, distributed and consumed, and the massive food production and processing system we have today serving large urban population centers did not yet exist. After mid-century, however, as more Americans began to concentrate in cities, it became more important to rely on sophisticated food processing and preservation technologies, including the use of specific food ingredients, to provide consumers with the wide range of appealing, safe, affordable and convenient foods they were seeking.

Food ingredients, as outlined in a brochure produced jointly by the FDA in collaboration with the International Food Information Council⁵, provide a range of technical functions in food. We have adapted several basic points from this brochure below:

1. *To improve or maintain safety and freshness:* Preservatives slow product spoilage caused by mold, air, bacteria, fungi or yeast. In addition to maintaining the quality of the food, they help control contamination that can cause foodborne illness, including life-threatening botulism. One group of preservatives—antioxidants—prevents fats and oils (and the foods containing them) from becoming rancid or developing an off-flavor. They can also help prevent fresh cut fruits, such as apples, from turning brown when exposed to air.
2. *To improve or maintain nutritional value:* Vitamins, minerals and other components such as fiber are added to many foods to make up for those that might be lacking in a person's diet, that may be lost in processing, or to enhance the nutritional quality of a food. Others ingredients are used to help lower the calorie or fat content of foods. Such fortification and enrichment has helped reduce malnutrition in the U.S. and worldwide. All products containing added nutrients must be appropriately labeled.
3. *Improve taste, texture and appearance:* Spices, flavors, and sweeteners are added to enhance the taste of food. Food colors maintain or improve appearance. Emulsifiers, stabilizers and thickeners give foods texture and consistency. Leavening agents allow baked goods to rise during baking. Some ingredients help control the acidity and alkalinity of foods, while others help maintain the taste and appeal of foods with reduced fat content. Furthermore, implicit in the use of any additive is that the use accomplishes a specific technical effect in the food. Title 21 of the Code of Federal Regulations (21 CFR Section 170.3(o)) contains a listing of definitions of physical and technical effects of food additives that help give insight into the various purposes for which additives can be used. In addition, "Good Manufacturing Practices," which apply to the production of any food or use of a food ingredi-

"food and color" additives where appropriate, we focus our regulatory discussion primarily on food additives, taking up issues relative to color additives only in certain examples where it is instructive.

⁴ Note that meat and poultry products (and processed egg products) are covered separately from other foods by the Federal Meat Inspection Act of 1906, the Poultry Products Inspection Act of 1957, and the Egg Products Inspection Act of 1970, as currently amended. These federal laws, however, defer to the FD & C Act for the establishment of safety standards for additives and ingredients used in meat and poultry products, and the FDA reviews the safety of additives and other ingredients used in these products as well. See: <http://www.nationalaglawcenter.org/assets/crs/RS22600.pdf>.

⁵ See IFIC Brochure: <http://www.cfsan.fda.gov/~dms/foodic.html>.

ent, dictate that the amount of an ingredient used does not exceed that which is required to achieve the desired technical effect. Overall, however, it is worth incorporating ingredients in food for the purposes outlined above only if these ingredients themselves have been demonstrated to be safe for their intended uses. FDA's food ingredient oversight and new food additive premarket review processes are designed to assure such safety.

3. What does the law require before a new food additive can be marketed?

- The Food Additive Definition and the "GRAS Exemption"

Section 201(s) of the FD&C Act defines a "food additive" as "...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. ...if such substance is not *generally recognized* among experts qualified by scientific training and experience...to be safe under the conditions of intended use."⁶ (*Emphasis added*) Because of its all-encompassing breadth, the first phrase, the so-called "component part" of the food additive definition, would seemingly include an infinitely large set of potential substances as food additives. Congress in its wisdom realized that such an inclusive definition, while correctly drawing a large universe of materials and their uses within its sweep, would, unless limited in some sensible way, also require many ostensibly safe food ingredients, some already in common use for years or millennia, to undergo premarket approval from the FDA. Spending public resources for this purpose would neither protect public health effectively nor make good public policy. Congress' solution was to add the latter clause, the so-called "GRAS exemption" to the food additive definition, where the acronym "GRAS" refers to the terminology "Generally Recognized as Safe."⁷ We discuss the GRAS concept and FDA's administration of it later in this paper.

- The Meaning of "Safe"

The 1958 Food Additives Amendment placed new food additives under a strict premarket approval regimen and safety standard. Prior to marketing, new food additives are presumed to be *unsafe* for their intended uses unless and until they are proven "safe" on the basis of scientific data and information. The burden of proof of safety lies with the petitioner. The petitioner must assemble and present to the agency in the form of a petition, all

⁶ The food additive definition in Section 201(s) also includes the so-called "indirect" food additives, or those substances whose use brings them into contact with food (for example, through food packaging) where their food additive status derives from their intentional use in contact with food and the inevitable migration of various components unintentionally into food. From 1958 on, the FD & C Act treated these materials as food additives themselves even though they were commonly called "indirect food additives." As such they required the full-blown filing, review and approval of a food additive petition in order to be lawfully used in the United States. After the passage of the FDA Modernization Act of 1997 (FDAMA) and the allocation in fiscal year 2000 by Congress of adequate funding to implement the new statutory changes, FDA instituted a premarket notification program for such "food contact substances" that obviated the need for a full-blown premarket petition review prior to marketing. In this new system, a company may notify the FDA 120 days prior to marketing and—if there is no FDA objection—go to market. FDA still requires that premarket notifications for food contact material uses contain the same quality and quantity of information previously applicable to indirect additive petitions, but the whole process is now greatly streamlined. In this paper we will not discuss this class of materials further.

⁷ See: FD & C Act section 201(s). We discuss the GRAS exemption in more depth in a later section of this paper and include there a discussion of the specific GRAS regulations in 21 CFR 170.30 and 170.35 as well as the April 19, 2007, GRAS reform proposal.

relevant safety data (both that which supports safety and that which may not) concerning the proposed use of the additive.⁸

FDA's chemists, toxicologists and other scientists, working on behalf of all citizens, review these data and independently ascertain whether the submitted data package as a whole supports the safe use of the additive as requested by the petitioner.

This FDA safety review includes consideration of: (a) the probable intake of the additive; (b) the cumulative effect of all uses of the additive; and (c) the relevant toxicological data needed to establish its safety. FDA's judgment about whether to approve a new food additive for a particular use, after a "fair evaluation of the data,"⁹ depends solely on whether the anticipated use satisfies the law's safety standard of "reasonable certainty of no harm."¹⁰

Unlike the approval of new drugs, the law for food additives does not permit FDA to consider "benefits" from the use of the additive in its decision—rather; it is a safety *per se* standard. Furthermore, unlike industrial chemicals and pesticides, food additives are generally

members of a class of chemicals of relatively low toxic potential, i.e., they have relatively little acute toxicity. Rather, the adverse effects of interest to FDA safety reviewers are usually more subtle and likely to be observed most clearly in animal feeding studies only after a lifetime of exposure (24 months typically). Ultimately, once approved, food additives must be safe for everyone—children and the very young; teenagers and adults; the elderly; pregnant and lactating women. It is assumed that every population subgroup may potentially be exposed to the additive in their diet, and possibly for their entire lifetime. If the use of an additive that is safe for most consumers could present special risks for certain subpopulations, such as those who might be allergic to a particular ingredient or who may have an inborn metabolic deficiency such as phenylketonuria, for example, then FDA can require special labeling so those consumers are properly informed. In addition, unlike the case of drugs, FDA promulgates "generic" regulations for food additives, not a "product-specific" approach as with drugs. Except for the case where a use of an additive is protected by a patent, any company that is in compliance with the conditions of use of the additive specified in the permitting regulation in the Code of Federal Regulations (CFR) may use the additive in food in the way prescribed and within the purview of that regulation.

⁸ The statute at 409(c)(5) states: "In determining, for the purposes of this section, whether a proposed use of a food additive is safe, the Secretary shall consider among other relevant factors—

- (A) the probable consumption
- (B) the cumulative effect
- (C) safety factors which in the opinion of experts qualified by scientific training and experience to evaluate the safety of food additives are generally recognized as appropriate for the use of animal experimentation data."

FDA's regulations at 21 CFR Section 171.1 specify the petition contents. Once a petition is received that has all the necessary elements for review, it is "filed formally via a notice in the Federal Register. This is a "formal rulemaking process under the Administrative Procedure Act, which means there is an opportunity for an administrative hearing following FDA's issuance of a food additive regulation.

⁹ The FD & C Act states (Section 409(c)(3)) that action on any petition requires a "fair evaluation of the data..." FDA has always interpreted this to mean that it should consider *all* the information pertinent to the safety evaluation of a food additive use, including that which is supportive of safety and that which may not be. The agency needs to see "the whole picture" prior to making a safety decision. This view is supported by the legislative history to the FD & C Act in which the Congress stated, "The committee feels that the Secretary's findings of fact and orders should not be based on isolated evidence in the record, which evidence in and of itself may be considered substantial without taking account of the contradictory evidence of equal or even greater substance..." (Committee on Interstate and Foreign Commerce, 85th Congress, 2nd Session, July 28, 1958.)

¹⁰ The FD & C Act states that a food additive must be "safe" prior to being marketed, but Congress did not define the term "safe." Congress did, however, provide further guidance in the legislative history of the Act wherein it stated, "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," (House of Representatives Report No. 2284, 85th Congress, 1958.) FDA, in regulations issued subsequent to the passage of the statute (21 CFR 170.3(i)) codified the definition of "safe" as follows: "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." Thus, the standard is, in fact, a "reasonable certainty of no harm" standard, where harm is "harm to health." Over the years, FDA officials have written much on what the reasonable certainty of no harm standard means and does not mean. One thing it does *not* mean is, "Certainty of no theoretical possibility of harm." In the end, however, the standard as applied must indeed ensure safety. It results in decisions inevitably made without absolute certainty, but always based on a fair evaluation of all the data. Application of the standard must, in the end, protect public health, where any residual uncertainty is not out of line with what has been previously considered acceptable in the context of all previous similar safety decisions. (Notably, the so-called "Delaney Clause" of the Act explicitly prohibits the approval of any additive shown to cause cancer in man or other animals. The food additive Delaney Clause, one of three such clauses in the Act [the others applying to color additives and animal drugs respectively], states in part at Section 409(c)(3)(A), that, "no additive shall be deemed to be safe if it is found to induce cancer when ingested by man or animal..." FDA's safety decisions on food additives do not weigh "benefits" of any kind (it is a safety *per se* standard) and are not intended to limit or enforce consumer choices among safe foods. Finally, the safety standard as applied must be able to withstand scientific, procedural and legal challenges from all sides. FDA's decisions based on this standard have consistently done this for the past fifty years, virtually without exception.

4. What information does FDA require to be submitted and reviewed?

FDA requires petitioners to submit a range of different types of information in a petition for the use of a new food additive. These include chemistry data elements detailing the chemical identity of the material and its purity and other technical specifications, as well as information about the environmental effects¹¹ that may result from the use of the material. By far, the two most important types of information that must be in any petition are: (1) data that allow FDA scientists to estimate the probable dietary intake levels of the additive resulting from its use in food (the so-called Estimated Daily Intake¹² or EDI); and (2) the data that allow the determination of the Acceptable Daily Intake¹³ (ADI) of the additive, i.e., the intake level in humans that may be safely consumed for a lifetime by virtually any member of the population without health or safety concerns.

5. How does FDA conduct its safety assessments?¹⁴

To perform its safety assessments on food additives, FDA assembles teams of scientists from within the Office of Food Additive

¹¹ The latter information is required because under the National Environmental Policy Act (NEPA) official actions by any federal agency, including an FDA approval of a new food additive use, requires a consideration of the environmental effects of that action.

¹² See: <http://www.cfsan.fda.gov/~dms/opa2cg8.html>, and references cited therein.

¹³ Much has been published over the years on the definition of the Acceptable Daily Intake (ADI) and its interpretations and limitations. The concept was first introduced in the late 1950s in the Council of Europe and by the World Health Organization (WHO)/ Food and Agriculture Organization (FAO) of the United Nations and in their subsidiary body, the Joint Expert Committee on Food Additives (JECFA) Several helpful primary references include the following: <http://www.ific.org/publications/qa/adiqa.cfm>; [http://www.eoearth.org/article/Acceptable_daily_intake_\(ADI\)](http://www.eoearth.org/article/Acceptable_daily_intake_(ADI)); and http://europe.ils.org/publications/Monographs/ADI_FoodSafety.htm. Other helpful secondary sources among many include the following: (E. Poulsen, 1995; Renwick and Walker, 1993.)

¹⁴ It is useful to distinguish between the terms "safety assessment" and "risk assessment" in the context of FDA food additive review. The former is a methodology for arriving at safe intake levels for food ingredients based on application of safety factors to "no-observed-adverse-effect levels" (NOAEL's) and "highest no-effect levels" (HNEL's) as originally outlined by Dr. Arnold J. Lehman and Dr. O. Garth Fitzhugh of the Food and Drug Administration (Lehman, 1959); whereas risk assessment in the most general sense is a broad set of methodologies focused on assessing the relative or absolute level(s) of risk associated with particular chemical or microbial hazards. The latter comprises a vast literature and an evolving set of methodologies that have been outlined over the years by several authoritative bodies such as the U.S. National Academy of Sciences (National Academy of Sciences, 1983), and the World Health Organization (World Health Organization, 1995) and continues to evolve.

Safety (OFAS) who have a range of different types of expertise. A typical review team consists of: (a) one or more chemists to review chemical identity and consumer exposure information on the additive; (b) toxicologists who study and evaluate the safety tests that have been conducted on the new additive¹⁵, including any animal feeding studies to determine safe levels of intake of the additive for humans, and who also may review clinical studies in healthy individuals to elicit information about actual human reactions to exposure of the new additive under controlled conditions; and (c) “consumer safety officers” (CSO’s) who, as scientists in their own right, are responsible for managing the overall review process to assure that the required data have been submitted, the appropriate questions have been asked and answered by all the responsible individuals, and that there is a complete written administrative record to document the agency’s entire safety evaluation process. It is also the CSO’s responsibility to draft the initial *Federal Register* document describing FDA’s decision on any food additive review, whether it is an approval or a denial. It is also possible that the review and judgment of a medically trained expert is needed. In that case, OFAS maintains a medical officer to advise in the review of clinical data and other pertinent information for which human medical experience is required. OFAS also maintains a staff of environmental scientists to review the environmental implications of the agency’s actions as required by the National Environmental Policy Act (NEPA).¹⁶

At the end of the review process, an appropriate scientific expert will have reviewed every pertinent data element in the petition, and the conclusions of that review will be recorded in the permanent administrative record of the petition. It is also noteworthy that during the review period certain aspects of the petition data (especially the toxicological studies that are under review, but not the agency internal evaluations themselves) are subject to release to interested parties under the provisions of the Freedom of Information Act (FOIA).¹⁷

The ultimate decision about whether to approve a use of a new food additive is delegated to the Commissioner of the FDA and those working on the Commissioner’s behalf. The Commissioner’s decision, however, must rest on the administrative record assembled as a result of the FDA review team’s work. To ensure the integrity of the process, FDA senior managers are responsible to assure that all relevant data are reviewed; that those reviews are documented in the administrative record; and that the opinions of all qualified agency experts are considered. The views of any given single person must not be allowed to dominate the conclusions of the agency in a manner out of proportion to, and irrespective of, the valid opinions

¹⁵ Note that the petitioner must conduct the toxicological studies on a new food additive. This expense is not borne by the general public. Many often wonder why the federal government does not conduct such tests itself. The answer is that Congress decided that the cost of testing new food additives that ultimately will be marketed should be borne by the private sector, and that federal scientists should, at taxpayer expense, be hired to review and evaluate independently the data in such studies on behalf of the public to determine whether the studies support the safety of the intended use of the additive. Furthermore, today studies conducted in support of the safety of a new food additive must be performed in accord with, and conform to the requirements of, “Good Laboratory Practices” that are established in FDA regulations in 21 CFR Part 58. What FDA brings to the process is scientific expertise, objectivity, and the ability to rule “up or down” based solely on the scientific data. This is not unique to food additives. FDA plays exactly the same role with respect to the review of new drugs, biological products and medical devices.

¹⁶ On occasion, the FDA review team will decide to request support from experts outside the Office of Food Additive Safety, including statisticians or epidemiologists from within CFSAN; other CFSAN and/or agency medical doctors with expertise in areas not in OFAS; or other expertise from within FDA or elsewhere in the federal government. Also from time to time, the agency will convene a food advisory committee or consult with individual nongovernmental experts on a particular food additive safety question. This type of review is discussed later in this paper.

¹⁷ Subsequent to the final decision the agency’s official memoranda evaluating the petition contents are also available for review under the FOIA.

(sometimes differing opinions) of the rest of the team. This doctrine assures that the professional views of all scientists reviewing the safety of a food additive are heard and become part of the administrative record of the safety review.¹⁸

6. How does FDA determine probable intake (i.e., Estimated Daily Intake, EDI) of the additive?

FDA requires that a petitioner describe the intended use and technical effect of the new additive in food, and in particular, information about the estimated actual use levels of the additive in the foods in which it will be used. Using this information, FDA chemists estimate the probable consumer intake of the additive under its intended conditions of use. The probable intake estimate arrived at by FDA chemists is the result of three principal factors, namely: (a) the amount of the additive to be added to particular foods; (b) the frequency with which consumers will eat those foods; and (c) the amounts of those foods consumed by individuals across the various subpopulations of consumers stratified by age groups.¹⁹ The calculation of probable intake is based on conservative assumptions about the additive, including the assumption there will be 100% market penetration and replacement of all additives in a given additive class by the new additive. The EDI is usually based on the 90th percentile estimate of the population of eaters of the foods to which the additive will be added. FDA also assumes that all population subgroups, including small children, adolescents, adults, the elderly, and pregnant and lactating women will be consuming the additive. In the end, the EDI represents a very conservative estimate (i.e., if anything, an overestimate) of the likely intake of the additive over a lifetime of the vast majority of individuals.

7. How does FDA determine safe levels of intake (i.e., the Acceptable Daily Intake, ADI) of the additive?

The ADI is a more complex quantity to determine, because it is usually derived from animal feeding studies and often requires the analysis by FDA scientists of many volumes of test data submitted by the petitioner. The data that FDA requires to support the safety of an additive with considerable population exposure, such as an intense sweetener, for example, comprises the following types of studies, at a minimum:

- Short-term tests for genetic toxicity
- Metabolism and pharmacokinetic studies
- Short-term toxicity tests in rodents
- Sub-chronic toxicity tests with rodents (usually 90 days in duration)
- Sub-chronic toxicity tests with nonrodents (usually 90 days in duration)
- Reproduction studies with a teratology phase to determine the potential of the additive to induce reproductive toxic effects or adversely affect any of the reproductive organs or reproductive systems of an animal, or produce birth defects of any type
- One-year toxicity tests with nonrodents

¹⁸ This approach is consistent with the expressed views of the Congress in the legislative history to the 1958 Food Additives Amendment to the FD & C Act, in which it states, “The committee has endeavored to prescribe a new statutory criterion requiring that a high standard of fairness be observed in administrative rulemaking under this bill. Personal attitudes or preferences of administrative officials could not prevail on the basis of being supported by substantial evidence picked from the record without regard to other evidence of probative value in the record.” (Senate Report on the Food Additives Amendment of 1958, 85th Congress.) This approach is also consistent with the statutory doctrine of “fair evaluation of the data,” in the FD & C Act, Section 409(c)(3).

¹⁹ See FDA guidance documents available at: <http://www.cfsan.fda.gov/~dms/opa-addi.html>.

- Chronic (lifetime duration, i.e., 24 months, typically) toxicity and carcinogenicity studies with rodents

FDA has published its recommended protocols for all the above types of studies in guidance documents such as the well known “Redbook,” or “Toxicological Principles for the Safety Assessment of Direct Food Additives and Color Additives Used in Food.”²⁰ In brief, the FDA toxicologists review the submitted studies, including the raw data. They independently ascertain which adverse effects occur at which animal doses and confirm the exposure levels associated with “no adverse effects.”²¹ Based on an analysis of the dose–response data, FDA scientists will determine the exposure levels that can be considered “without adverse effect” in the most sensitive, longest-duration studies applicable to the analysis. This exposure level is often referred to as the “highest no-effect level” or “HNEL” for the additive.

Typically, FDA then applies a “safety factor” of 100-fold (10-fold to account for the fact that the data were obtained from feeding studies conducted in test animals, not humans, even though they will be applied to humans, and an additional 10-fold to account for normal genetic variations and the range of susceptibilities that is possible across the human population). FDA has employed this 100-fold “safety factor” approach for many decades,²² and it has proven to be reliably protective of public health. The HNEL, when multiplied by the safety factor of 1/100, is thus reduced 100-fold to an exposure level to the additive that is considered to be without potential for adverse health effects in humans over their lifetimes and consistent with the statutory standard of “reasonable certainty of no harm.” This intake level of the food additive (i.e., the HNEL multiplied by the 1/100 safety factor) is assigned as the Acceptable Daily Intake (ADI) of the additive.²³

The agency then compares the ADI it obtains from the above calculation to the EDI to confirm that the petitioned use of the additive will not result in a human dietary exposure (using the EDI as a benchmark) that exceeds the ADI. Over the years, a number of more sophisticated techniques have become available for performing quantitative risk assessments. These include computer assisted quantitative structure–activity analysis; low-dose extrapolation models and curve fitting to laboratory data; modern statistical techniques that explicitly consider the systematic and random errors inherent in laboratory measurements; the proper use of historical control data in analyzing animal feeding study data; the importance of comprehensive histopathology analysis in discerning the nature of the adverse effects observed in a study, and whether an observed effect is indeed actually “adverse,” and therefore can be associated with a decrement in health; and many more. When making food additive safety decisions, FDA reviewers may consider applying one or more of these techniques, but at the

end of the process, the invocation of the simple ADI/EDI comparison has been found consistently to be an adequate and effective approach to reaching a final decision on the safety of a given additive.

8. What special animal studies, human clinical studies, or other specialized considerations does FDA employ?

Sometimes the standard toxicological test regimen based on animal feeding studies will not elucidate all the biochemical or toxicological phenomena adequately to resolve a potential safety issue in regard to the use of a particular additive. For example, questions may arise concerning the nature, extent and fate of one or more metabolites of the additive in the test animal or human gastrointestinal tract. In such a case, special radio-tracer studies using ¹⁴C radiolabeled molecules may be required to quantify the picture. Or, the issue of the stability of levels of blood glucose in diabetics ingesting a particular sugar substitute may be at issue. Or, the additive may be unpalatable to the test animals and it must be fed to pairs of animals (in a so-called “paired feeding study”) whose diets can then be compensated for any decrease in calories ingested because of the unpalatability of the test substance. These types of studies are often undertaken by petitioners (many times at FDA’s request) to clarify an outstanding issue of public health importance.

Today petitioners are increasingly developing new types of food additives that have the potential to substitute for major caloric components of the diet, such as sugar substitutes, fat substitutes, or as sources of fiber. Because such substances may be ingested in relatively large amounts compared to traditional additives, their toxicity potential in the traditional sense must be quite low, and it usually is low. Such additives may possess the potential, however, to elicit other types of effects that also have safety implications. In such situations, conventional toxicology studies may not be able to get at the safety issues of concern. As a result, petitioners are making increased use of alternative types of safety information, including clinical data, to support the safety profiles of these new types of additives. Rather than focusing on the common endpoints of classical toxicology studies such as: (a) gross weight–gain effects or organ-to-body-weight ratio effects; (b) frank toxic responses such as organ and/or cellular damage; or (c) reproductive or teratogenic effects; the effects of concern may be more subtle physiological types of responses, or have nutritional consequences rather than toxicological ones. Alternatively, there may be issues relating to the potential allergenicity of an additive that must be resolved prior to making a safety decision.

When such issues arise (e.g., including nutritional safety, the need to demonstrate the lack of allergic potential of an additive, or the potential of the additive to interact with certain prescription medications) they can turn out to be as important, if not more important, than the traditional toxicological ones in reaching a final decision on the safety of the use of the additive. In those cases, the petitioner may need to design special studies, including clinical studies, to inform this part of FDA’s safety review. For its part, FDA will often involve medical doctors to review data gathered in the clinical setting.

Clearly, the data from nutritional studies, drug interaction measurements, blood glucose homeostasis evaluations, allergenicity potential, or data from other special types of studies are not amenable to a straightforward EDI/ADI safety evaluation comparison. A more multifaceted approach to judging safety involving a range of issues beyond the scope of the simple EDI/ADI comparison is required. This “multifaceted” approach, focused on the weight of evidence from other relevant safety-related information, is increasingly becoming part of the normal regimen of safety review for FDA’s scientist–evaluators.

²⁰ The Redbook is a publication of the U.S. Food and Drug Administration (FDA). Note that the studies recommended comprise just the minimum list of studies. More may be needed to clear up ambiguities or inconclusive results. Also special studies may be needed to resolve specific issues. See the FDA Website at: <http://www.cfsan.fda.gov/~redbook/red-toca.html> (FDA, 2000).

²¹ A premise of toxicological testing is that materials should be fed to test animals over a range of doses which at some level(s) are *intended* to induce an adverse effect. Only in this way can it be determined which doses cause *no* adverse effects. Thus, the appearance of adverse effects in toxicity studies is a mark of success in elucidating the nature and extent of toxic potential of a substance, not, as some imply in the popular media, proof that the substance is “toxic” at all doses. Throughout this process, FDA reviewers are mindful of the ancient maxim of Paracelsus that it is “the dose that makes a thing a poison,” and that virtually any substance can be shown to elicit adverse toxic effects if the dose is sufficiently large. Thus substances are not “toxic” *per se*, except in relation to their administered doses. (Paracelsus, 1564).

²² FDA pioneers in this area were Arnold J. Lehman and O. Garth Fitzhugh. (Lehman, 1959) This approach is also codified in the U.S. Code of Federal Regulations at 21 CFR 170.22, “Safety factors to be considered.”

²³ See footnote 10 and the associated references on the origin and definition of the Acceptable Daily Intake (ADI).

8.1. Olestra as a case study

A prime example of a food additive safety review that relied on a broader array of safety considerations was FDA's review of Procter & Gamble's (P&G's) fat substitute olestra.²⁴ Traditional toxicological studies performed on this fat substitute (a sucrose polyester molecule formed by the chemical combination of common sucrose with six, seven, or eight fatty acids) showed little or no frank toxicity in the traditional sense. This is partly because the olestra molecule is not inherently chemically reactive in the human gastrointestinal tract; i.e., it is largely impervious to enzymatic attack and digestion in either humans or test animals. However, this fact did not result in a simple or trivial safety review. While there were no indications of conventional toxicity, ingestion of the material was found to result in other effects relevant to FDA's judgments on the safety of the compound in use.

Even though olestra's chemical inertness causes it to pass through the GI tract virtually intact, FDA reviewers realized that other physiologically important effects must be considered in its safety evaluation as a result of this unique property of olestra. For example, the presence of olestra with its fat-like physical properties in the GI tract may lead to the physiological effect of loose stools along with possible attendant cramping. (such effects were reported in clinical studies performed by the petitioner). While FDA's evaluation eventually dismissed the possibility that the loose stools are truly diarrhea in the clinical sense (with concomitant water and electrolyte loss), the physical phenomena that could occur still required FDA to evaluate their potential to be of health significance to consumers. As a result, FDA evaluated clinical studies conducted by the petitioner to elucidate the nature and extent of such effects, and their dependence on the amount and frequency of olestra ingestion.

In the same way, the agency evaluated concerns about the potential of olestra to trap fat-soluble food constituents such as fat-soluble vitamins from the GI tract (because olestra is itself a fat-like molecule) and eliminate them via the feces before they could be absorbed by the body. As a result, FDA required that the petitioner conduct and present to the agency analyses of this effect, and to determine the degree to which olestra-containing foods might need to be supplemented with fat-soluble vitamins in order to compensate for any vitamin loss that could occur as a result of this simple physical phenomenon. In its approval decision, FDA determined that olestra-containing foods should be required to contain *added levels* of the fat-soluble vitamins A, D, E, and K, above those normally present in the foods themselves, to compensate for possible interference with the absorption of these vitamins from the digestive tract that could occur as a result of their partitioning into the olestra phase during digestion.

Because of the complexity and extent of the data amassed on this new food additive (including much information in areas of safety having little to do with establishing a traditional ADI for an additive, but which were still important to consumers' health and safety), FDA reviewers devoted cumulatively thousands of hours of review time to the safety evaluation of this food additive.²⁵ In addition, at the time of approval, the petitioner agreed to gather, and report to FDA, both passive and active post-approval sur-

veillance data on olestra, focusing on both the possible physiological as well as the nutritional effects described above.²⁶

Thirty months after the approval of olestra, the FDA, as stipulated in its approving regulation for olestra, reconvened its Food Advisory Committee to review and evaluate all the data and information bearing on the safety of olestra that had been received by the agency since the initial approval in January 1996. This second olestra advisory committee meeting was held June 15–17, 1998. As a result of that public review, FDA confirmed its original conclusion that the use of olestra is safe, and that its use is still consistent with the safety standard of reasonable certainty of no harm.

Furthermore, following an extensive review of all the newly-gathered surveillance data, data and information brought before the second Advisory Committee meeting, and data submitted to the agency in a petition²⁷ to amend the olestra regulation, the FDA concluded, in a final rule²⁸ published in August 2003, there was no basis for extending the temporary advisory label on olestra-containing foods that the agency had required since its original approval of olestra in 1996. The decision to eliminate the label statement was based on the FDA's review of more than five years of research and data gathering, including clinical studies conducted among people eating olestra-containing snacks under real-life conditions, post-marketing surveillance, a recommendation by the second olestra Food Advisory Committee, and input from the public.

(Other examples of post-approval data gathering for other additives and food ingredients are described in a later section of this paper.)

8.2. Sucralose as a case study

Another example of a multifaceted safety review for a prominent new additive is FDA's evaluation of the sweetener sucralose (Splenda®).²⁹ This sugar substitute underwent the full-blown pre-market safety evaluation required of any new food additive entering the U.S. food supply. The review included the normal analysis of chemical identity, estimates of probable intake, and the detailed results from a range of toxicological safety studies. As in the case of olestra, FDA's review of sucralose went beyond the conventional information requirements to include other issues. For example, during the sucralose review process, FDA received requests from outside parties to examine the toxicological information available on sucralose *at the same time* the agency was reviewing it (this is permitted because, as we noted above, the toxicological data submitted by a petitioner in a food additive petition is not exempt from release under the Freedom of Information Act, even before the agency has reached its final safety decision). Unsolicited comments on safety studies from outside parties were received on more than one occasion, and sometimes these comments contained new data interpre-

²⁴ FDA ultimately concluded that the GI physiological effects as described in studies submitted by the petitioner did not constitute a hazard to health. FDA, however, wanted to obtain further information and reports from individuals about the nature and extent of these physiological effects in actual use, in order to confirm that such effects are indeed recognized by consumers and that consumers can and will adjust their intake of olestra-containing snacks to mitigate or prevent any effects they might experience. In addition, to monitor the effectiveness of FDA's required vitamin restoration levels in the marketplace and under conditions of actual use, P&G gathered post-approval surveillance data shortly after olestra's approval in 1996, and for many months thereafter. These active-surveillance data included blood samples from volunteers (to determine serum vitamin status and serum carotenoid levels). P&G reported these data to the agency on a regular basis, and also presented them to the agency's food advisory committee. This surveillance work confirmed the validity of the agency's original premarket safety judgments for this new member of the class of "macro" food ingredients.

²⁷ Notice of Filing of a Food Additive Petition in the *Federal Register* of March 3, 2000 (65 *FR* 11585).

²⁸ Final Rule published in the *Federal Register* of August 5, 2003 (68 *FR* 46364).

²⁹ "Food Additives Permitted for Direct Addition to Food for Human Consumption; Sucralose," 63 *Federal Register* 16417-16433; April 3, 1998.

²⁴ See: *Federal Register* 61, 3118-3173, January 30, 1996. Also see transcripts of FDA Advisory Committee meetings on olestra, November 14-17, 1995 and June 15-17, 1998, respectively.

²⁵ FDA evaluated more than 150,000 pages of data drawn from more than 150 studies; conducted two 3-day advisory committee meetings; and consulted with numerous subject matter experts during and after the petition's review.

tations to which the agency ultimately had to respond in its final rulemaking, in addition to its own evaluations. Furthermore, at more than one juncture in the course of its review, agency scientists themselves raised their own questions about the data submitted in the petition, requiring the petitioner to conduct additional studies at their own expense to clarify some potentially ambiguous interpretations from previously performed studies.

One particular issue related to an unexplained body-weight-gain decrement observed in the growing rodents fed sucralose in one set of long-term feeding studies. It required the petitioner additional time to carry out definitive supplemental studies and FDA to conduct a subsequent agency review before agency scientists were convinced that these safety-related issues were resolved. Finally, as the agency's review process drew to a close, the petitioner made the agency aware of additional data that had just recently been developed arising from its experience with the additive's use abroad. It concerned whether diabetics consuming the additive would be able to maintain stable blood glucose levels when ingesting foods containing the additive. The petitioner rightly concluded that the agency should be made aware of these new data prior to making its final safety decision. As a result, the agency subjected these data to rigorous statistical analysis, including referring them to experts in the agency's Center for Drug Evaluation and Research, before concluding that the new data did not impugn the safety of the petitioned uses of sucralose.

The agency's review of the above issues for sucralose, including descriptions of the review of the safety studies originally submitted in the petition, are described in detail in the agency's final *Federal Register* order approving sucralose (*Federal Register*, 1998). The final order, of course, also covers the issues normally of interest in any complete safety evaluation of a major new food additive, including the pharmacokinetics and metabolism of sucralose in animals and humans; genotoxicity testing; reproductive and developmental toxicity studies; teratology studies; chronic toxicity and carcinogenicity studies in rats and mice; chronic toxicity in dogs; the special studies addressing body-weight-gain issues described above that were ultimately resolved by FDA reviewers; immunotoxicity studies in rats; neurotoxicity studies in multiple species; and, finally, the studies described above that focused on blood glucose homeostasis in the diabetic population. Based on a thorough analysis of all the above data, FDA's reviewers concluded that sucralose was safe for the intended uses requested in the petition.

9. How do food ingredients qualify for "GRAS status and how does FDA administer the "GRAS Notice process?"

As we noted above, the FD & C Act exempts from premarket approval those food ingredients that qualify for the food additive definition but whose use is generally recognized as safe (GRAS), (i.e., for which there is a general recognition by qualified³⁰ experts that these ingredients are safe for their intended uses). The so-called "GRAS exemption" to the statutory definition for food additives in Section 201(s) of the FD & C Act expresses Congress' recognition that many commonly used food ingredients, some with long histories of safe use in food or whose safety based on scientific procedures is widely recognized and accepted by qualified experts, need not be subjected to further government scrutiny. As we pointed out above, in the absence of such an exemption, the wide reach of the "compo-

nent part" of the food additive definition in the Act would needlessly require many common and ostensibly safe food ingredients and their uses to become the subject of new food additive petitions.

The GRAS exemption has been much misunderstood and misinterpreted over the years. Others have provided cogent insights (see for example, *Degnan*, 1991). Many people mistakenly associate GRAS with a sort of "second" tier of safety protection, based on a less-than-rigorous standard compared to petitioned food additives.³¹ This is not true. In fact, the safety standard applicable to GRAS food ingredients is the *same* as for food additives, namely "reasonable certainty of no harm." What the statute does not provide, however, is an easy-to-follow roadmap describing precisely how one satisfies this standard for GRAS ingredients, other than to say that they must either have a long history of safe use in food by a sufficiently large population of eaters, or that, based on scientific procedures there is a consensus among experts qualified by scientific training and experience to judge such matters that the use of the ingredient is safe.³²

What truly distinguishes GRAS ingredients from food additives is *information* in the form of *common knowledge* about the safety of the substance for its intended use, and in addition, the *general availability* and *general acceptance* of that information across the scientific community of food ingredient safety experts. An excellent source of information on the history of the GRAS concept and the agency's implementation of programs to assist food manufacturers in making their decisions about the GRAS status of food ingredient uses, is the April 17, 1997, *Federal Register* proposal published by FDA to reform the GRAS process (*Federal Register*, 1997).³³

In that document, FDA not only reviewed the regulations defining GRAS and administering the GRAS process, but also proposed replacing the then-existing voluntary but resource-intensive GRAS Affirmation Petition process the agency put in place in the 1970's, with a more streamlined voluntary GRAS notification process. In the 1997 notice, the agency made it clear that both food additives and GRAS ingredients require the same strength of evidence of safety. For food additives, the FDA reviews and approves the use based on evidence supplied by the petitioner in the form of a petition. For GRAS ingredient uses, the *extra* added element is the general recognition required that the available safety evidence is both widely known (e.g., available in the published literature or in commonly accessible knowledge sources such as text books) and that there is a consensus among qualified experts about that evidence in support of the safe use of the material in food. In fact, the GRAS criteria are in some ways more difficult to satisfy than the food additive criteria because of the *additional requirement* of public availability of the data and general recognition and acceptance of a safety conclusion based on those data. For GRAS ingredients, although there may not always be a need for an extensive set of toxicological tests that support the safety of the use of the substance (as is usually the case for food additives), especially if the material is a common constituent of normal bodily fluids, or is

³⁰ Congress did not specify any explicit requirements or criteria that define or determine whether an expert is "qualified" under the terms of this statutory criterion. The Congress has left this judgment up to the agency. FDA would normally look for such qualifications as training and experience in the relevant scientific disciplines, professional positions held, name recognition by fellow members of the scientific community and publications in respected journals in the field.

³¹ This perception in part results from the food additive petition requirements' placing the burden on the petitioner to provide all safety information to the agency for its review and decision *before* the additive may be lawfully used in food. This clear placement of the burden of proof is a formidable barrier, particularly if the agency, as it may often do, asks the petitioner for new or clarifying information beyond what it originally submitted, and the process is extended for a lengthy period thereafter.

³² Currently, the regulations in 21 CFR 170.3 and 21 CFR 170.30 state that the use of a food ingredient may be GRAS either through "scientific procedures" or have a history of safe use in food prior to 1958. These regulations state that to be GRAS an ingredient requires the "same quantity and quality of scientific evidence as is required to obtain approval of the substance as a food additive and ordinarily is based upon published studies, which may be corroborated by unpublished studies and other data and information." General recognition through experience based on common use in foods [prior to 1958] requires "a substantial history of consumption for food use by a significant number of consumers."

³³ Ref. *Federal Register* (1997).

ubiquitous in nature and its biochemistry well known, the so-called “common knowledge element” of GRAS (i.e., scientific evidence supporting safety under the conditions of use) still must be satisfied. Moreover, the requirement for the knowledge to be widely known and accepted by scientists is itself a significant additional requirement.³⁴ Normally, the mechanism used to establish that the necessary scientific information is generally available is to show that the information is published in a peer-reviewed scientific journal. The agency points out, however, that,

“publication in a peer-reviewed scientific journal of data (such as toxicity studies) on a test substance has been used to establish expert consensus in addition to general availability. In other cases, such publication of data and information in the primary scientific literature has been supplemented by: (1) publication of data and information in the secondary scientific literature, such as scientific review articles, textbooks, and compendia; (2) documentation of the opinion in an “expert panel” that is specifically convened for this purpose; or (3) the opinion or recommendation of an authoritative body such as the National Academy of Sciences (NAS). . . .”

These distinctions are discussed in FDA’s 1997 *Federal Register* notice (*Federal Register*, 1997). The FDA also accepts, as part of a GRAS notification, unpublished studies as providing additional support for or corroboration of the published scientific findings, but the critical data and information forming the essential basis of a GRAS determination must be in the public domain.

This GRAS notification program has operated for more than a decade. During this time the agency has received and responded to well over 200 GRAS exemption claims on a wide range of food ingredients, many within the agency’s target time frame of 180 days (Gaynor et al., 2006). As a technical matter, when FDA responds affirmatively to a GRAS notice, it summarizes the data relied upon by the notifier and states that the agency has “no questions at this time about (the notifier’s) conclusions that the material is GRAS under the intended conditions use,” and further states that the agency has, “not made its own determination regarding the GRAS status of the subject use.” This format was adopted because, under the law, it is the notifier’s burden of proof to establish the GRAS status of the compound. The agency does not officially “approve” a GRAS notice like the agency does for a food additive petition. This distinction is due to the nature of the GRAS exemption. Implicit in the agency’s response that it has no further questions is the point that the agency believes the notifier has made a sufficiently strong case that the use of the substance in food: (a) satisfies the reasonable certainty of no harm safety standard, and (b) that the knowledge base concerning that safety is generally available and generally accepted by a consensus among qualified experts. In practical terms, when FDA does not disagree with the notifier’s GRAS determination, it is in effect saying that it is comfortable that the case has been made that the proposed use of the substance in food as described by the notifier poses no safety issues, and that the general scientific community would agree.

The existence of some controversy does not disqualify a GRAS conclusion. A GRAS claimant, however, should fully address in a GRAS notice any controversies and differences of scientific opinion and interpretation that might exist and be prepared to respond to these later in detail should they arise. The concept of a consensus among qualified experts does *not* mean there must be *unanimity* of

³⁴ The FDA’s 1997 proposal states that, “The common knowledge element of the GRAS standard includes two facets: (1) The data and information relied on to establish the technical element (evidence of safety) must be generally available; and (2) there must be a basis to conclude that there is consensus among qualified experts about the safety of the substance for its intended use. Neither facet, by itself, is sufficient to satisfy the common knowledge element of the GRAS standard.”

opinion about the safety of the use of a GRAS substance. What interests FDA and the general food safety community is that, in the written basis for the GRAS conclusion, the notifier should be able to demonstrate satisfactorily that the points of controversy that do exist have been addressed with specificity, and neither any one separately, nor all collectively, pose a credible challenge to the GRAS conclusion. When substantial credible criticisms of a GRAS claim go unanswered by those asserting GRAS status for an ingredient use, it has the potential to cast a cloud over the GRAS claim because the claim is, by definition, based on *general awareness and general acceptance by qualified expert consensus*. Moreover, if there is a “severe conflict”³⁵ among qualified experts on the safety of the ingredient for its intended use, that would preclude a finding of GRAS.

Although many GRAS notices receive a positive response from FDA, the agency has not been reluctant to conclude, when appropriate, that the notifier has not adequately established the safety and/or the general recognition of the safety of an intended use. Unless a deficient GRAS notification is withdrawn, the Agency completes that process with a publicly available letter to the notifier indicating that the notification has deficiencies so that the agency’s rejection of the notifier’s GRAS claim is documented and fully transparent.

10. When does FDA consult with experts from other FDA centers or from outside FDA?

Occasionally, FDA finds that it must call upon knowledgeable experts in particular fields to obtain additional expertise before making a decision on an additive. For example, in some cases the FDA may wish to access specialized medical expertise not available within the Center for Food Safety and Applied Nutrition. Or, the agency may need to resolve a question about the physiological effects of an additive on the human gastro-intestinal tract. In that case, FDA might consult with an expert on pediatric gastroenterology. Such consults are often accomplished by calling in a single expert on a particular subject for a targeted discussion on the topic. These experts may come from another FDA Center, such as the Center for Drug Evaluation and Research, from another federal agency, or from academia. If the expert is from outside government, the expert will be retained as a “special government employee” (SGE) a status that is subject to the government’s strict conflict-of-interest requirements. Results of all such deliberations become part of the administrative record of agency decision-making.

11. When does FDA employ advisory committees in its decision-making?

Occasionally, FDA will make use of the combined judgment of multiple experts to resolve specific questions concerning the safety of a food additive. In such a case, FDA may convene an advisory committee to provide additional expertise or new perspectives to the agency’s review, or to permit more public participation in the review process.³⁶ Such committees consist of experts in appropriate fields relevant to FDA’s questions concerning the additive. These experts are selected from a pool of candidates willing to serve the government in the SGE role. Potential candidates for FDA advisory committee membership are screened for conflict-of-interest. Advisory committees usually have access to the same materials that FDA scientists have reviewed, and they usually have access to FDA’s evaluations for their own reference. Typically, the advisory committee

³⁵ See the FDA GRAS proposal, 62 *FR* 18939 for a discussion of the notion of “severe conflict” among experts.

³⁶ This must be done in conformance with the Federal Advisory Committee Act (FACA), 5 U.S.C. App. 2 § 1 (2000).

is asked, in light of all the submitted information and other information to which they have access, whether they believe that the agency scientists have covered all relevant aspects of a safety evaluation, leaving no important issues unresolved. The committee may also be asked to make recommendations to FDA on whether a food additive meets the agency's safety standard. Transcripts of advisory committee meetings become part of the administrative record of a petition review, and the deliberations of the advisory committee, including any votes taken on controversial scientific points, are additional elements that may be considered part of the weight of evidence on a new additive that the agency can factor into its decision-making process.

12. The food additive final order: The regulation as legal brief

As noted above, before a new food additive can reach the marketplace, FDA must first issue a regulation prescribing the conditions under which the additive may be safely used. Initially, the burden is on the manufacturer or user of the additive to submit the petition requesting that a permitting regulation be issued, and the petition must contain the necessary supporting information about the safety of the substance in the context of its intended use. Once the petition has been submitted and the petition reviewed by FDA and an ADI determined for the new use of the food additive, the FDA review team drafts a technical memorandum summarizing the agency's conclusions about the safety of the proposed use of the additive. If the agency decides to approve the use of the additive, the team then also drafts the final rule that is the authorizing regulation in accordance with the formal rulemaking process as defined in the Administrative Procedure Act (APA).³⁷

Formal rulemaking means that, even after FDA issues an authorizing regulation, interested parties may object, submit scientific data on which their objections are based, and request a hearing before the FDA. The FD & C Act specifies that the agency, when approving a new food additive use, shall, "by order establish a regulation (whether or not in accord with that proposed by the petitioner) prescribing, with respect to one or more proposed uses of the food additive involved, the conditions under which such additive may be safely used. . . ."

- The final rule as a thorough scientific explanation of the agency's decision.

Over the years, it has become the norm for FDA's final regulation on a new additive use to contain an extensive preamble in addition to any new CFR sections that codify a new use of the food additive or deny a petitioned use. The preamble, based on the administrative record of the agency's petition review, lays out in careful detail, the information that the agency reviewed in its safety evaluation, including chemical identity, purity and specification information, estimates of human exposure resulting from the proposed use of the additive, and all the toxicological tests performed on the additive along with an overview of the findings of those tests. The preamble describes how the agency assessed all the relevant information and reached its conclusion about the new food additive use in question, supporting each statement with relevant references from the administrative record of the petition review.

- The final rule as a legal brief in support of an action that may come under procedural and judicial challenge.

The final regulation, with its explanatory preamble, thus can serve as a core element of a legal defense, should the agency's deci-

sion ever become the subject of litigation. If that should happen, the agency has readily available references to all the data it reviewed, the decision points it reached on each of the relevant data elements, and a full explanation of how, on the basis of this analysis, the agency concluded as it did regarding the additive use. In essence, the final order permitting the new use of the food additive provides the same support to the agency as a legal brief in arguing a case. FDA's adherence to this procedure has enabled the agency to respond effectively to any challenges to its safety decisions during the post-approval period.

13. What happens after FDA approves a new food additive?

In the majority of situations, FDA's judgment about the safety of a new use of a food additive stands unchallenged—both as a matter of law and of science. In some cases, however, a food additive approval by FDA is not the end of the story. On occasion post-approval hearings are requested, or new data are presented that may challenge FDA's original conclusions. In some cases much public debate and discussion may surround the approval or the proposal to ban a use of a controversial additive. There are many prominent examples of additives that have evoked controversy after (and sometimes even before) FDA had approved their use. For some additives, controversies persist for months and even years.^{38,39} In this section we discuss aspects of the post-approval period, looking at some of the administrative procedures that govern post-approval actions by FDA; how and why the agency may decide on its own initiative to gather post-approval data for additives; and how the agency responds to controversies surrounding

³⁸ The sweeteners saccharin and cyclamate are two prominent examples. Since its discovery in 1878 by Constantin Fahlberg in the laboratory of Professor Ira Remsen at Johns Hopkins University, saccharin has been at center stage of many controversies. Those before 1958 have been described in detail by FDA historian Suzanne Junod (1994), who, in her Ph.D. thesis, describes the disagreement between FDA's Harvey Wiley and President Theodore Roosevelt over the sweetener. In 1977, the FDA proposed to ban saccharin on the basis of the reported carcinogenicity results of animal feeding studies, and because of the agency's view that the Delaney Clause of the Act required such a ban. FDA's proposed ban of the sweetener was overridden by a Congressional moratorium (passed as the "Saccharin Study and Labeling Act" on November 23, 1977). This law also required health warning labeling on all saccharin-containing food products, and requested a study of saccharin's safety by the National Academy of Sciences. In 2000, the National Institute for Environmental Health Sciences, in its National Toxicology Program "Report on Carcinogens—9th Edition," removed saccharin from the list of substances "reasonably anticipated to be a human carcinogen." Saccharin was removed from this listing on the basis of a determination that bladder tumors that had been observed in rats, "arose from a mechanism that is not relevant to humans." Also in 2000, Congress repealed its 1977 requirements for special saccharin labeling. Cyclamate, discovered at the University of Illinois in 1937, and placed on the original GRAS list of food ingredients in 1958, was the subject of an FDA ban in 1969, based also on carcinogenicity issues. Subsequently, the sweetener was repetitioned before FDA, but that petition is still pending.

³⁹ The case of color additives provides a richly textured history of post-approval data gathering, hearings, safety re-evaluations, risk assessments, proposals to ban, and other regulatory, administrative and scientific machinations that have persisted for many years and in some cases took literally decades to resolve. As stated above, this paper focuses on food additives, not color additives, so we provide here only a listing of some of the more notable color additive rulemaking issues that have arisen over the years and that could suffice to form the basis for an entirely separate publication. Many issues began as Congress passed the Color Additive Amendments in 1960, and several color additives in use at the time were placed on a "provisional list" where re-testing and re-evaluation of safety was required before the additives could be "permanently listed" for use as safe color additives. From 1960 to well into the 1990's, prolonged agency re-evaluation of one or more of the following color additives has occurred: FD & C Red No. 2, where the issue was whether the available data were sufficient to resolve whether the color induces cancer in test animals; FD & C Red No. 3 where the agency unsuccessfully argued that the cancer risks identified in animal feeding studies were *de minimis* and therefore should not result in a ban.; FD & C Blue No. 2 where issues of carcinogenicity were again central; FD & C Yellow No. 5 and Yellow No. 6 where issues of allergenicity were prominent; FD & C Green No. 5 where the FDA's Carcinogenic Impurities policy was tested and was successfully upheld in the courts.

³⁷ Administrative Procedure Act, 5 U.S.C. § 551 (2000).

additives, both among members of the scientific community and in the popular media.

13.1. Post-approval administrative procedures and hearings

Once the FDA Commissioner or designee sign a final order approving a new food additive use and it is published in the *Federal Register*, the regulation has the force and effect of law. For a relatively short period thereafter, the FD & C Act and FDA's regulations provide a range of post-approval administrative remedies, including stays, public formal evidentiary hearings, hearings before a public board of inquiry or before the FDA Commissioner, and ultimately, the opportunity for judicial review in the courts.⁴⁰ Even in the long-term, FDA's regulations provide the option for anyone to submit a Citizen Petition challenging any regulation currently on the books.⁴¹ After FDA makes its final decision on an additive use, however, the threshold for changing course is quite high, and depends greatly on the timely presentation of convincing supporting data, as we discuss below.

13.2. Post-approval monitoring of food additives by FDA

There are two distinct modes in which FDA engages in the monitoring of food additives after approval. First, there is the short- to medium-term post-approval period in which the agency may request *ad hoc* surveillance data on specific additives. This is often arranged with the petitioner in a voluntary way, but may be fully integrated into the approval process. The second mode is a more general long-term monitoring of relevant safety information on all approved additives over time, and is carried out on the initiative of the agency and uses the agency's resources.

A) Post-approval surveillance and ad hoc data gathering

In some cases, FDA determines that the approval of a new food additive ought to be followed by gathering additional information after the additive enters the marketplace. This is done primarily to confirm that agency's original safety decision, made on the basis of animal studies and estimates of human dietary intake, continue to be supported by actual experience. The agency has used this approach in cases where the subject additive is a novel ingredient or is a member of a class of ingredients for which there is little experience in the marketplace, or for which the exposure margins between the ADI and EDI may be particularly close.

As described above, FDA estimates the daily intake of an additive (EDI). These estimates are quite conservative, and the safety margins employed are sufficient to ensure that there will be no public health risk from the new use of the additive. Still, it is possible, though unlikely, that the actual dietary exposure to an additive for some population subgroup(s) may be greater than FDA had originally estimated. This could occur for example, if there were higher than expected consumer demand for food products containing the additive (such as in the case of a new intense sweetener, for example). In such cases, especially if the margin between the ADI and EDI is relatively narrow, the FDA may request, at the time of approval, that the petitioner continue to collect information after approval to more precisely determine the true consumer exposure to the additive under actual use market conditions. In this way, the

agency is able to confirm or alter the original premarket estimates upon which the agency based its original safety determination.⁴²

- Case studies: Aspartame, Benecol® and Take Control® as examples
 - Aspartame

The regulatory history of the sweetener aspartame is complex and the details are beyond the scope of this paper. Briefly, however, the original petition for this dipeptide intense sweetener was limited to use in dry foods and chewing gum. When objections were filed to its approval, FDA stayed the approval and convened a Public Board of Inquiry (PBOI)⁴³ under the administrative regulations of 21 CFR Part 13. After the PBOI returned a split recommendation⁴⁴ in 1980–81, then FDA Commissioner, Dr. Arthur Hull Hayes, reinstated aspartame's approval, stating, "Few compounds have withstood such detailed testing and repeated close scrutiny."⁴⁵ At the time of its approval for use in soft drinks in the early 1980's, FDA received the agreement of the petitioner, G.D. Searle Co., (later to become NutraSweet Company) that it would gather data on actual intake levels resulting from aspartame ingestion, and report these data to FDA. This was done, as was noted above, to help confirm that the intake of aspartame in actual use did not exceed the ADI.

Searle contracted with the Market Research Corporation of America (MRCA) to survey actual aspartame intake by consumers. This work began in 1984 and continued for about eight years, after which it was capped off by one or two additional *ad hoc* single-year surveys of aspartame intake.⁴⁶ These data were received and analyzed by FDA, and confirmed that FDA's original exposure estimates were sufficiently conservative, in that actual consumer exposure levels did not exceed those originally projected, nor did they even come close to the ADI.⁴⁷ FDA approved aspartame for general food use in 1996. Recently, several authors have published a comprehensive review of the safety of aspartame, including an analysis of exposure information and toxicological and epidemiological data.⁴⁸

◦ Benecol® and Take Control®

In 1999, McNeil Consumer Products and Unilever both approached the FDA concerning their intention to market the spreads Benecol® and Take Control® respectively as dietary supplements capable of maintaining healthy serum cholesterol levels. FDA considered these products to be foods, not dietary supplements, requiring their active ingredients, stanol esters and sterol esters,

⁴² Aspartame was monitored for years and data submitted to FDA by Nutrasweet. Actual data showed that the agency's original EDI was high, thereby increasing still further the actual margin of safety.

⁴³ A Public Board of Inquiry (PBOI) is a panel of outside scientific experts, specifically provided for in FDA's procedural regulations, to hear an appeal and make specific findings and conclusions. Any decision by the PBOI may be appealed, in turn, to the Commissioner of Food and Drugs for a final agency decision. A hearing before a PBOI is an alternative to a hearing before an administrative law judge and has been used by the FDA when the issues involved are viewed to be more scientific than legal in nature.

⁴⁴ The PBOI voted 2:1 against approval. This decision was reviewed and reversed by the Commissioner upon appeal under the Part 13 hearing procedures.

⁴⁵ 46 FR 50947 (October 16, 1981) and <http://ncseonline.org/nle/crsreports/pesticides/pest-5.cfm>.

⁴⁶ See Food Master File FMF 261, U.S. Food and Drug Administration and the NutraSweet petition for expanded uses of aspartame in Food Additive Petition 5A4439.

⁴⁷ Personal communication with Dr. David Hattan, toxicologist, FDA Office of Food Additive Safety, November 2007, and information in: <http://www.ncseonline.org/nle/crsreports/pesticides/pest-5.cfm> (Vogt, 1995).

⁴⁸ "Aspartame, a Safety Evaluation based on Current Use Levels, Regulations and Toxicological and Epidemiological Studies," B. A. Magnuson, et al; *Critical Reviews in Toxicology*, 37: 629–727, 2007.

⁴⁰ Post approval procedural actions are governed by regulations in 21 CFR Part 10, and 11–16. These CFR Parts provide mechanisms for parties to challenge the agency's actions, and under the formal rulemaking procedures applicable to food additives, provide opportunities for various types of formal evidentiary and other hearings before a case may be brought to judicial review in a court of law.

⁴¹ Citizen Petitions: rules are laid out in 21 CFR 10.30.

respectively, to be looked at as food ingredients by FDA. Consequently, McNeil and Unilever each, independently, submitted information to the agency for evaluation as GRAS notification submissions. The agency reviewed the submitted material and sent favorable letters to the companies regarding their scientific conclusions that their respective products were safe and lawful for their intended use. In FDA's letters to the companies, however, the agency requested that the firms gather data on actual consumer use and quantitative human exposure levels to their products (and thus indirectly the compounds of interest) to confirm that exposures to these substances were not exceeding original estimates.

- B) Long-term monitoring of additives: GRAS review, cyclic review and the priority-based assessment of food additives (PAFA)

Because science itself is always a dynamic process, safety decisions based on a given dataset at one point in time may need to be revisited in light of new data that become available at a later time. Years after an additive is approved, exposure levels might change significantly as a result of new use patterns. New toxicological information could become available, either reducing or raising concerns with regard to particular adverse effects. Over time, new types of studies might be developed to address questions that were not tractable when the original premarket approval safety review was conducted. Such data needs to be continually retrieved from the literature and needs to be continually integrated into the overall information base on food additives.⁴⁹

- The "GRAS Review"

FDA's first major systematic review of food ingredients based on this idea was the agency's review of Generally Recognized as Safe food ingredients, the so-called "GRAS Review." As we outlined above, Congress recognized in 1958 that not all food ingredients needed to be subjected to a full-blown premarket safety review. Shortly after passage of the Food Additives Amendment, FDA published (in December 1958) the first list of FDA recognized GRAS substances and then subsequently incorporated the list into 21 CFR Parts 182 (and later in Parts 184 and 186). FDA recognized that these published lists are not comprehensive of all potential GRAS ingredients, given that judgments about GRAS are not within the purview of FDA alone, but are also rightfully within the purview of other "qualified experts."

In 1969 and the early 1970's, when new data began to emerge that raised questions about the safety of certain long-marketed food additives, FDA initiated a systematic review of the safety of the substances listed on FDA's "GRAS list." This project, commonly called the GRAS Review, continued for many years in several phases. In 1972, the Life Sciences Research Office (LSRO) of the Federation of American Societies for Experimental Biology (FASEB) under contract to FDA, summarized the existing scientific literature for all the food ingredients in the review, and considered whether any new limitations should be placed on the use of particular GRAS ingredients to ensure their continued safe use. LSRO named a panel, called the Select Committee on GRAS Substances (SCOGS) to evaluate independently all the gathered information on several hundred GRAS ingredients. FDA made the SCOGS reports, including their recommendations concerning ingredient safety, publicly available (FDA, 2006). The formal GRAS review has since ended,

but one of its major legacies is a better-documented basis for the safety in use of a vast array of commonly used food ingredients (FASEB, 1977,1995; Fisher, 1977).

- Cyclic Review and PAFA:

In 1977, in Senate hearings chaired by Wisconsin Senator Gaylord Nelson, the Acting FDA Commissioner at the time, Sherwin Gardner, stated that FDA would extend the concepts of the GRAS review to all approved food and color additives.⁵⁰ As part of new appropriations to expand the agency's good laboratory practices regulations in light of a nonclinical laboratory testing scandal involving Industrial Biotech Laboratory,⁵¹ FDA hired a number of new employees in the late 1970's in part to conduct the new systematic review of the safety data supporting the food and color additives that the agency had approved up until that time.

The history of this "Cyclic Review" of food additives is well documented, and the results of its analyses have been published.⁵² As part of this work and as a continuation of the GRAS review described above, the agency, under a contract with the National Academy of Sciences, gathered information on the poundage of all approved food additives used annually in the U.S food supply. Combining this information with a review of the available toxicology data on each additive, both from FDA's own files and from literature searches under contract, FDA reassessed the safety margins for all approved additives.

FDA found, as a result of this work, that the vast majority of additives are comfortably covered by safety margins, usually far in excess of that normally required by application of the 100-fold safety factor to the latest studies. Virtually no additives were determined to have safety concerns based on the re-evaluation of existing data. These analyses were published in a series of four papers (Rulis et al, 1984; Rulis and Hattan, 1985; Rulis, 1987; Hattan et al, 1986).⁵³

14. What does FDA do when new data appear?

Questions about the continuing safety of food additives periodically arise in the scientific community, before regulatory agencies, and in the popular media. GRAS and/or "prior sanctioned"⁵⁴ ingredients such as monosodium glutamate, common table salt (sodium chloride), sulfites, antioxidants like BHA and BHT, and nitrites or caffeine, all come under continuing scrutiny.

It is interesting, however, that major interest seems to focus on intense sweeteners. This has certainly been true for saccharin and cyclamate, as noted above, and continues as well for several of the more recently approved sweeteners like aspartame. FDA expends considerable resources responding to inquiries from citizens concerned that sweeteners and other similar additives may be causing a range of maladies.

Some continuing concern is understandable, given the nature of risk perception.⁵⁵ We tend to have a lower tolerance for risks we perceive as imposed upon us by "anonymous manufacturers" or

⁵⁰ The Washington Star, Thursday, January 17, 1977, p. 1.

⁵¹ Industrial Biotech reference, see for example: <http://www.ibiblio.org/ecolandtech/SoilWiki/message-archives/JoeCummins/msg00440.html>.

⁵² Cyclic Review and PAFA Refs. Rulis et al (1984); Rulis and Hattan (1985); Hattan and Rulis (1986); Rulis (1987).

⁵³ PAFA Papers I-IV, published in *Regulatory Toxicology and Pharmacology*, summarized the findings of the FDA's Cyclic Review, examining the dependence of food additive toxicity on chemical structure category and distributions of effect doses in various types of animal feeding studies as a function of structure class (Rulis et al, 1984; Rulis and Hattan, 1985; Rulis, 1987; Hattan et al, 1986).

⁵⁴ "Prior Sanctioned" ingredients are defined in Section 201(s)(4) of the FD&C Act.

⁵⁵ See for example publications on risk perception and the sources of imposed risk, including: MacGregor et al., 1999; and Sandman, 2008 and Sandman at <http://www.psandman.com/index.htm>.

⁴⁹ Toxicology Forum presentation by George Pauli on the process for reevaluating previous agency decisions, Toxicology Forum Winter 2005 meeting in Washington, DC. (Pauli, 2005).

“market forces.” Nevertheless, in the highly charged atmosphere of food safety and additives in food, it is all the more important that any new data be subjected to transparent and impartial analysis and review.

In this environment, FDA continues to be alert to any new data that appear. Such new information could arise from many sources. For example, there could be well-designed studies conducted by a government agency somewhere in the world to better understand the safety issues surrounding a given additive. Sometimes new data could arise from research originating in a university laboratory, or an independent testing firm with no ties to either a government or the regulated industry. In some cases, such new data may confirm already accepted understandings about the safety of these additives. In other cases, the attendant publicity may simply raise public alarms about issues that were never a concern when FDA originally evaluated the additive for safety. There may also be legitimate findings of new and unanticipated risks.

FDA's approach to such new data on additives is to keep an open mind, of course, but also to insist on performing its own rigorous review of the data, as it did in the premarket phase. This requires the agency to be able to review any new data in detail, including the pathology slides from new studies. FDA will also insist on examining the protocols of any new studies so that the agency can verify for itself the conclusions of the study's authors. This is important, because, as a legal matter, the burden of proof is on those presenting the new study to prove any new conclusions about the safety of an additive that could change an additive's regulatory status. It is also important because of FDA's long standing tradition of looking at the evidence in its entirety, and not being swayed by one piece of evidence without full consideration of the entire body of evidence as a whole. The standard of evidence for data quality and quantity should be—and is—no less rigorous for new data than for data employed in the original approval package. This helps assure that FDA will draw proper risk management conclusions from new data and data interpretations that will continue to protect public health.

15. Summary and conclusions

It is common in our public media and popular culture today to hear many conflicting views and opinions voiced about the safety of the additives in our food, both before and after they receive a final opinion from the FDA. This can be confusing for the public, and may leave people wondering whether they may be at risk. In this paper, we have tried to provide an outline of the essential attributes of FDA's food additive safety review principles and procedures. Our purpose was to draw upon our first-hand experience with food additive safety review issues we encountered at FDA during our careers, and to make the case that FDA's guiding scientific principles as well as the administrative procedures it has in place ensure that the agency's decisions are of high integrity and scientific credibility. We believe that these are the rea-

sons that the agency's decisions are rarely, if ever, successfully challenged.

The FDA has a special responsibility to ensure that the foods we consumers purchase are not harmful to us or to our families. The agency has enjoyed a level of trust on the part of consumers who rightfully see it as a competent and impartial arbiter of food safety.

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