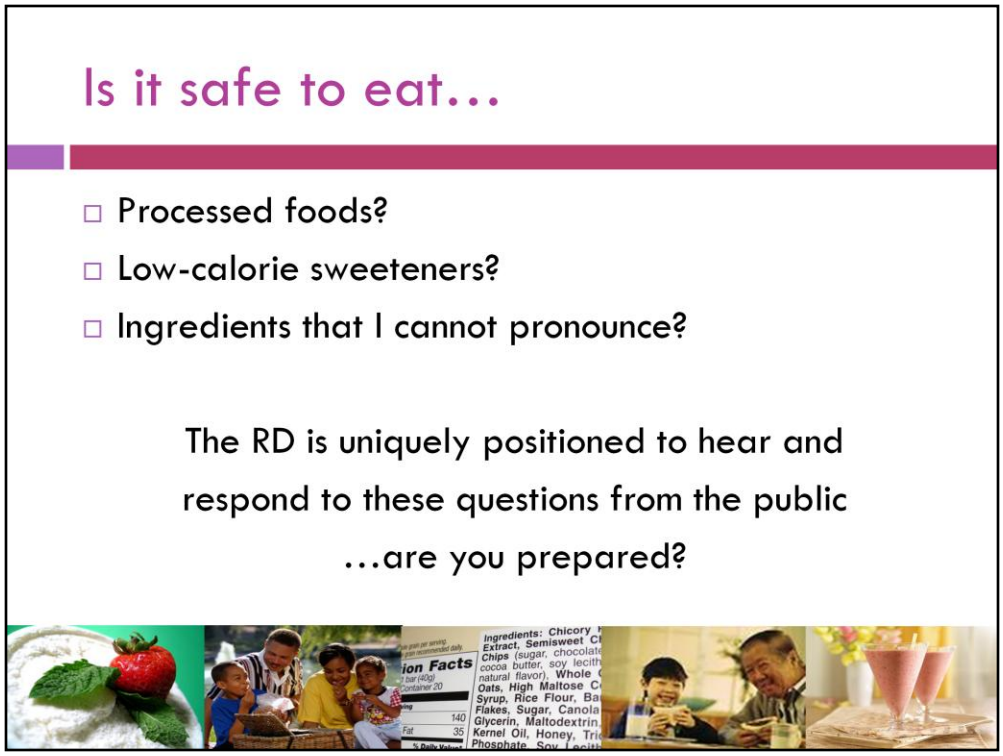
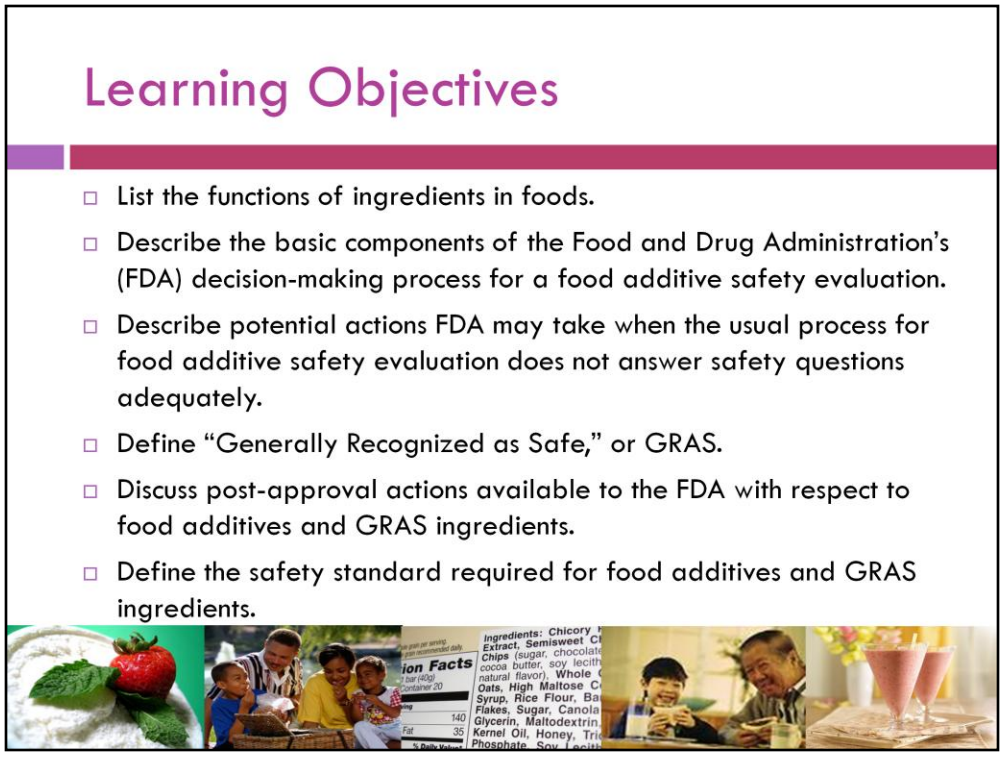
DEMYSTIFYING FDA'S FOOD INGREDIENT APPROVAL PROCESS

A self-study continuing professional education module for dietetic professionals



Dietitians and other health professionals hear the questions every day about whether the foods in grocery stores or restaurants are healthy and safe. Processed foods, complex ingredient names, low-calorie sweeteners, and preservatives are just a few examples of ingredient-related questions asked by consumers. The RD is uniquely positioned to hear these questions and respond to them, but must be prepared to do so.

The Calorie Control Council received a great deal of interest from RDs interested in learning more about food additive regulations, following its successful webinar provided in partnership with the Food and Culinary Professionals practice group in 2009. This module provides an in-depth exploration of the regulations for food additives.



After completing this continuing professional education module, learners will be able to:

- List the functions of ingredients in foods.
- Describe the basic components of the Food and Drug Administration's (FDA) decision-making process for a food additive safety evaluation.
- Describe potential actions FDA may take when the usual process for food additive safety evaluation does not answer safety questions adequately.
- Define "Generally Recognized as Safe," or GRAS.
- Discuss post-approval actions available to the FDA with respect to food additives and GRAS ingredients.
- Define the safety standard required for all food ingredients, including both food additives and GRAS ingredients.

In the era of the "clean label," the purpose of each ingredient in a food product is under great scrutiny. A historical perspective on the purpose of food ingredients and the substances used to process foods provides interesting context for today's food supply. Throughout the 20th Century, the United States has transitioned from a primarily agrarian to an urban society. The food system today serves large urban population centers around the globe, utilizing technology and ingredients that allow the production of foods with a wide range of appealing, safe, affordable, and convenient foods.

Why are Food Ingredients Used?

- Improve or maintain safety and freshness
- Improve or maintain nutritional value
- Improve taste, texture, and appearance
- Emulsify, stabilize, or thicken foods for texture and consistency

Food ingredients provide diverse technical functions in food, such as the following (http://www.cfsan.fda.gov/~dms/foodic.html):

- *Improve or maintain safety and freshness*: Preservatives slow product spoilage caused by mold, air, bacteria, fungi, or yeast, thereby helping to maintain food quality and prevent foodborne illness. One group of preservatives—antioxidants—prevents fats and oils (and the foods containing them) from becoming rancid or developing an off-flavor, and help prevent fresh cut fruits, such as apples, from turning brown when exposed to air.
- *Improve or maintain nutritional value*: Vitamins, minerals, fiber, and other components are added to many foods to make up for those that might be lacking in a person's diet or that may be lost in processing. Other ingredients, such as intense sweeteners, are used to help lower the calorie or fat content of foods. All products containing added nutrients must be appropriately labeled.
- *Improve taste, texture, and appearance*: Spices, flavors, and sweeteners are added to enhance taste. 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.

A little known fact is that federal regulations (21 CFR Section 170.3(o)) and ''Good Manufacturing Practices" actually define the physical and technical effects for which food additives can be used. Only an amount required to achieve the desired technical effect can be added. Of course, safety is the guiding goal of FDA's food ingredient oversight and new food additive premarket review processes.

Regulatory Authority

- The Food and Drug Administration (FDA) regulates the use of food additives
  - Authorized by Food Additives Amendment to the Federal Food, Drug, and Cosmetic Act (FD&C Act)
  - Including additives in meat and dairy products (otherwise regulated by U.S. Department of Agriculture)

In the case of food ingredients, responsibility to oversee safety, including the premarket safety evaluation of new food additives, rests with the FDA.

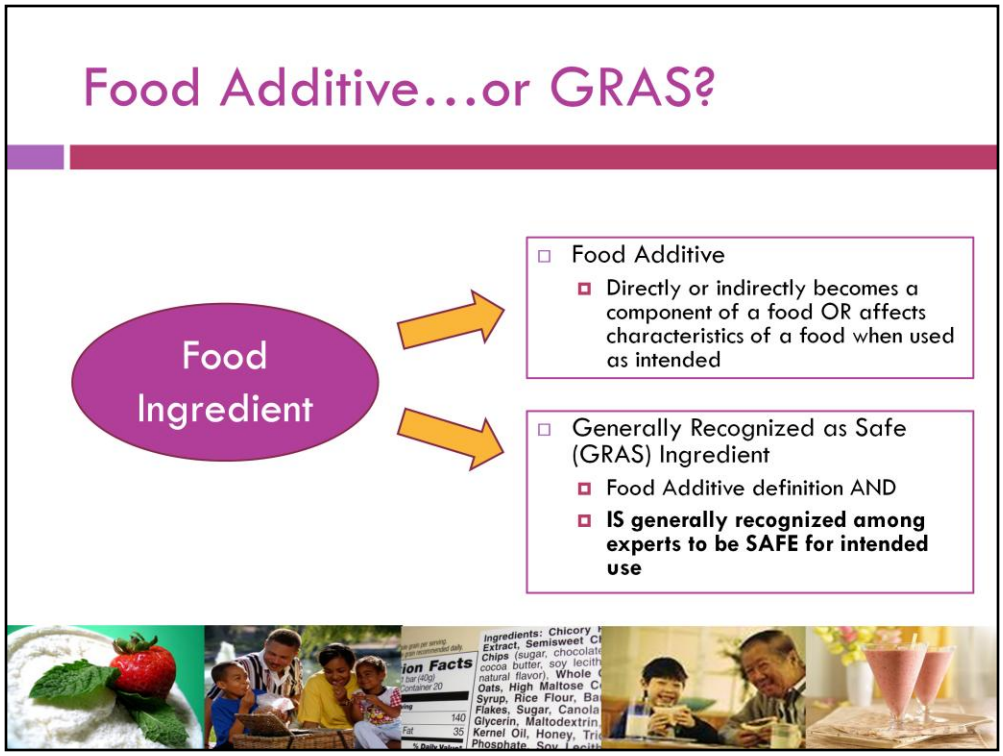
The FDA's role in food additive safety evaluation is authorized by the Food Additives Amendment to the Federal Food, Drug, and Cosmetic Act (FD&C Act) (1958). The Food Safety and Inspection Service (FSIS) of the U.S. Department of Agriculture shares responsibility for the safety of food additives in meat, poultry, and processed egg products with the FDA, although the FDA conducts the initial safety review and has ultimate regulatory authority for all food additives (FSIS, 2008).

The Meaning of "Safe"

- New food additives presumed *unsafe* until proven *safe* by the science
- Burden of proof is with the "petitioner"
- Safe defined as "reasonable certainty of no harm"
- Safe for everyone over a lifetime of use

Prior to marketing, new food ingredients are presumed to be unsafe for their intended uses unless and until they are proven "safe" on the basis of scientific data and information (Rulis and Levitt 2009). The burden of proof lies with the company that petitions the FDA, or the "petitioner." The petitioner must provide all safety data (both in support of or questioning safety) relevant to the proposed use of the additive in the form of a Food Additive Petition. If the ingredient in question is believed to be GRAS (Generally Recognized as Safe), a GRAS Notification may be filed.

Whether GRAS or additive, the anticipated use of the ingredient must meet the standard of ''reasonable certainty of no harm." Prior to additive approval or determination of GRAS status, food ingredients must be demonstrated to be safe for everyone—children, teenagers, adults, the elderly, and pregnant and lactating women. If the use of an ingredient that is safe for most consumers could present special risks for certain subpopulations, FDA requires special labeling to alert those consumers. An example of such an ingredient would be aspartame, which contains phenylalanine, an amino acid that cannot be metabolized properly by those phenylketonuria.



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" (Rulis and Levitt 2009). For food additives, the FDA reviews and *approves* the use based on evidence supplied by the "petitioner" in the form of a petition.

Many food ingredients have been safely consumed for generations, such as cinnamon or ascorbic acid. When the FD&C Act was written, Congress decided that requiring the FDA to conduct a full premarket approval of all food ingredients would divert resources for public health protection away from investigating new ingredients, and would waste public resources (Rulis and Levitt 2009). Therefore, ingredients that meet the definition of an additive but are ''*Generally Recognized as Safe*," or *GRAS*, are not considered food additives. In considering the GRAS status of an ingredient, the FDA evaluates the GRAS Notice (as submitted voluntarily by the "notifier") and either "responds affirmatively" or "rejects" it.

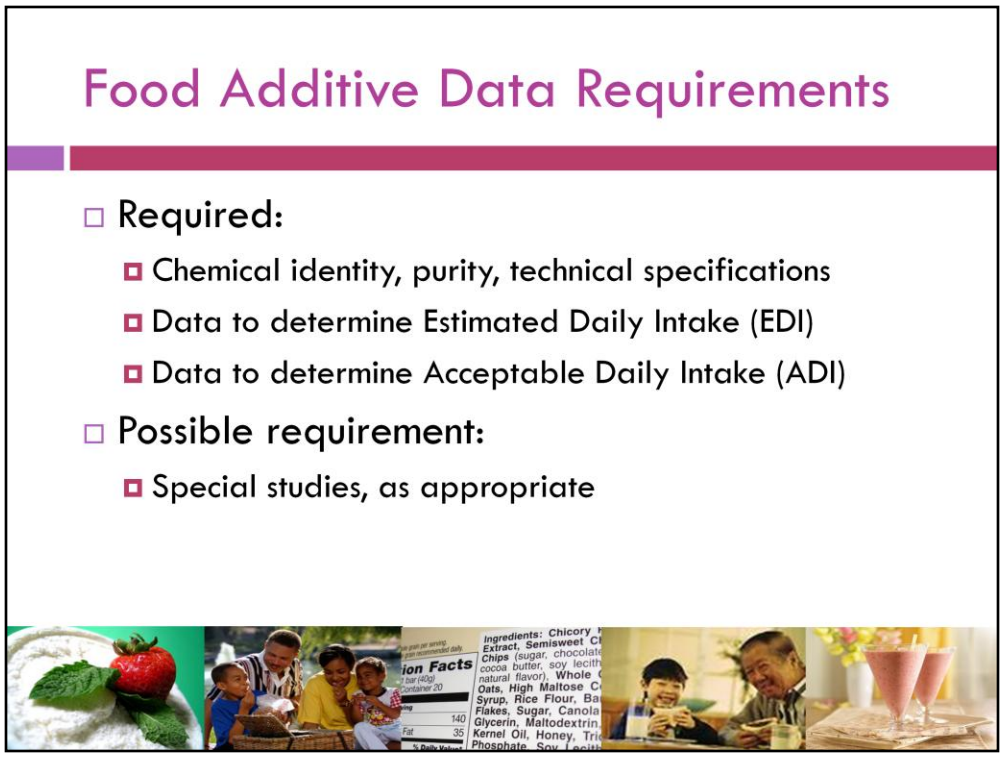
There is a perception that GRAS ingredients are not as tightly regulated as food additives (Rulis and Levitt 2009). At the request of Congress, the Government Accounting Office (GAO) published a report concluding that the FDA should strengthen its oversight of GRAS, although the Agency must operate within the limits of the FD&C Act (GAO 2010). The GRAS Notification, however, may in some ways be more difficult to compose than a Food Additive Petition (Rulis and Levitt 2009). Specifically, a GRAS ingredient must be safe over a lifetime of exposure, just as for a food additive (to be detailed in the following slides). In addition, the case for safety must be based on publicly available evidence, which may take decades to establish. Also, for either a GRAS Notice or a Food Additive Petition, the FDA's review does NOT allow for consideration of the benefits of using the substance.

Food Additive Scope of Review

- Probable intake of the additive
- Cumulative effect of all uses of the additive
- Relevant toxicological data needed to evaluate safety
- FDA NOT ALLOWED to consider "benefits"

The safety review of a food additive by the FDA includes consideration of:

- the probable intake of the additive over a lifetime by virtually any member of society;
- the cumulative effect of all potential uses of the additive; and
- the relevant toxicological data needed to evaluate safety (Rulis and Levitt 2009).



FDA requires petitioners to submit a range of information for the use of a new food additive.

- First, data detailing the chemical identity, purity, and technical specifications are required.
- Importantly, the petitioner is required to submit data that will allow FDA scientists to estimate the probable dietary intake levels of the additive resulting from its use in food (the Estimated Daily Intake or EDI), assuming 100 percent market penetration.
- Also required are data that will allow the determination of the Acceptable Daily Intake (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* (including the most vulnerable, such as those who are pregnant or lactating, children, the elderly, etc) *without health or safety concerns* (Rulis and Levitt 2009).

In addition, special studies may be provided to address questions unique to the particular food additive, or to clear up ambiguities that remain after evaluation of the ADI and EDI.

The FD&C Act designates that the cost of testing new food additives should be borne by the petitioner or others in the private sector, as they would eventually market the product. Studies conducted in support of the safety of a new food additive must be guided by the "Good Laboratory Practices" (GLP) established in the FDA Code of Federal Regulations (21 CFR Part 58).

On behalf of and at the expense of the public, the law also mandates that federal scientists should independently review and evaluate the data to determine whether they support the safety of the intended use of the additive (Rulis and Levitt 2009). This process is consistent with FDA's role in the review of new drugs, biological products, and medical devices. FDA assembles teams of scientists from within the Office of Food Additive Safety (OFAS) that typically consist of:

- one or more chemists to review chemical identity and consumer exposure information;
- toxicologists who study and evaluate safety tests (including animal feeding studies) to determine safe levels of intake 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
- ''consumer safety officers" (CSO's) who 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, whether it is an approval or a denial.

Insight is sought from other types of experts, as needed, including environmental scientists regarding the environmental implications of the agency's actions as required by the National Environmental Policy Act (NEPA), and/or medical officers regarding clinical data and other information for which human medical experience is needed (Rulis and Levitt 2009). For example, the agency may consult with a gastroenterologist to resolve a question about the physiological effects of an additive on the human gastrointestinal tract. Expertise outside of the core Expert Review Team may be found either within the FDA or with another federal agency or academia. Any expert from outside government is retained as a ''special government employee," subject to strict conflict of

interest requirements.

Food Additive External Advisory Committee

- Additional expertise or new perspective to internal Expert Review Team
- Permit public participation
- Strict conflict of interest requirements
- Scope of deliberations defined by FDA
- Conclusions included among elements FDA considers in decision-making

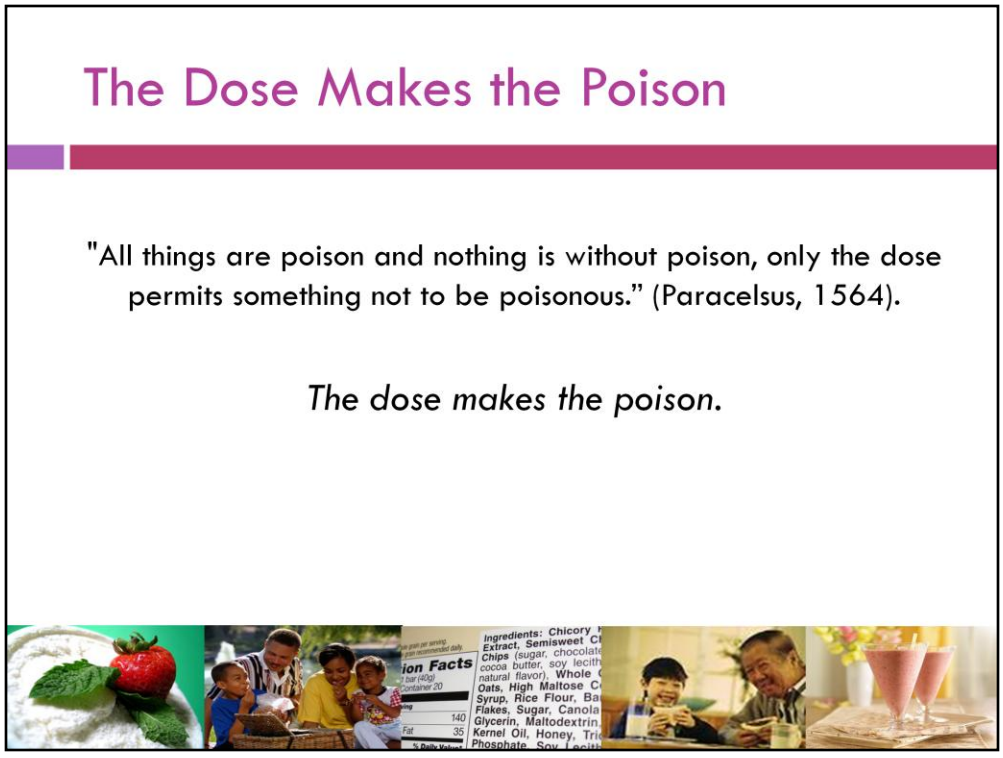
Occasionally, FDA will convene an advisory committee to provide additional expertise or new perspectives to the agency's review or permit more public participation in the food additive review process (Rulis and Levitt 2009). Such committees consist of experts in appropriate fields relevant to FDA's questions concerning the additive, and are screened for conflicts of interest. Advisory committees usually have full access to the materials reviewed and evaluations formed by FDA scientists in order to determine whether the agency scientists have conducted a thorough evaluation of safety of the food additive, and possibly whether a food additive meets the agency's safety standard. Advisory committee deliberations are additional elements that may be considered in the decision-making process.

Food Additive Safety Review Process

- Determine EDI
  - Amount to be added to particular foods
  - Frequency with which consumers will eat those foods
  - Amounts of those foods consumed, across subpopulations, stratified by age
  - Aiming for conservative estimate of likely intake over a lifetime of the vast majority of individuals, including most vulnerable

FDA requires a description of the intended use of the new additive in food, including the estimated levels to be used in each of the foods in which it will be used (Rulis and Levitt 2009). FDA then considers three factors: (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. The calculation of probable intake is based on several assumptions that ensure a conservative estimate of the likely intake of the additive over a lifetime of the vast majority of individuals, including the following:

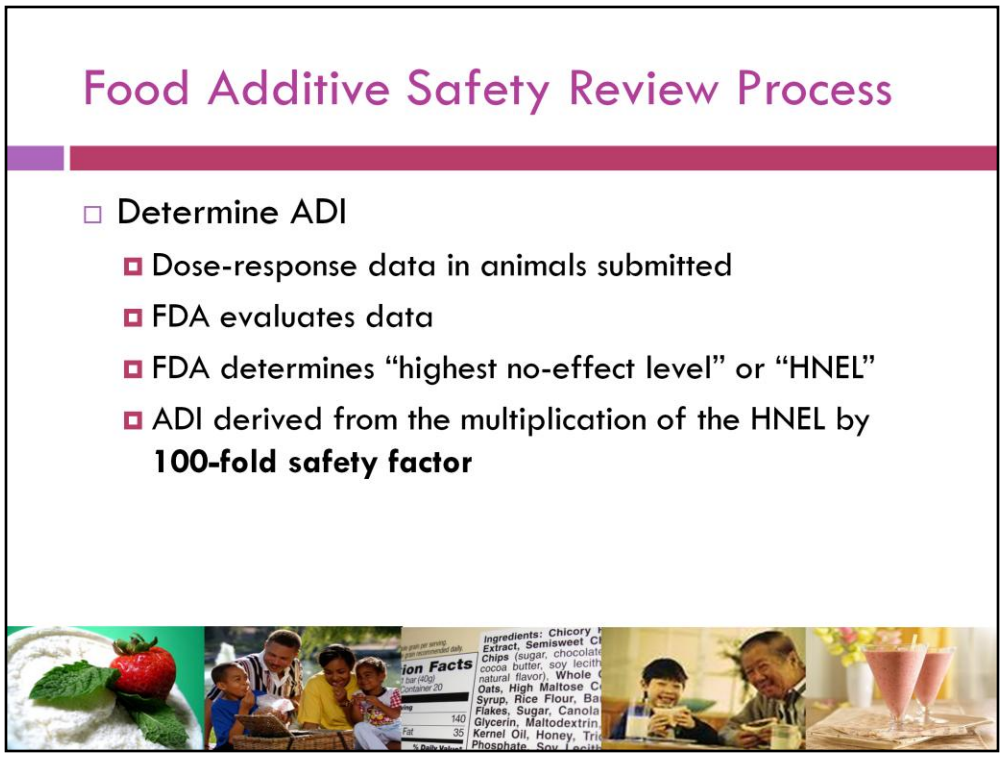
- There will be 100% market penetration and replacement of all additives in a given additive class by the new additive. For example, a sweetener would be assumed to replace all sugar or other sweeteners in the food supply.
- Population intake estimates of the foods to which the additive will be added is based on the 90th percentile of intake.
- All population subgroups, including small children, adolescents, adults, the elderly, and pregnant and lactating women, will be consuming the additive.



There is a common misperception that harm at a particular dose signals harm at any dose. Similarly, many assume that foods or ingredients that are beneficial are safe at any level of consumption. For most things that can be ingested, even water, vitamins, and minerals, too much or too little could be harmful. Therefore, the FDA requires the evaluation of exposures high enough to actually elicit harmful effects. Only by finding the level that causes harm, which exists for nearly everything, may the "no adverse effects" level be confidently documented (Rulis and Levitt 2009).

For obvious ethical reasons, such toxicological testing would not be conducted in humans. Therefore, animal feeding studies are critical for evaluating the effects of a range of doses of a potential food additive. The particular animal to be studied is a critical consideration in evaluating particular effects, based on similarities to and differences from human physiology and metabolism. Recommended protocols for research assessing safety for human food consumption are available in publications such as FDA's "Redbook" and "Toxicological Principles for the Safety Assessment of Direct Food Additives and Color Additives Used in Food."

A negative response at a certain dose does *not* imply that a substance is ''toxic" at all doses (Rulis and Levitt 2009). Even in the 16th Century, Paracelsus understood that the dose makes a substance poisonous, or not poisonous.



In order to determine the ADI, the FDA requires that the petitioner submit extensive documentation, including but not limited to the following types of studies (including raw data) (Rulis and Levitt 2009):

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

The FDA toxicologists independently review the animal data to understand the nature of adverse effects at various doses. Based on the most sensitive, longest-duration studies, FDA scientists will determine the "highest no-effect level" or ''HNEL" for the additive. This is the highest dosage or intake level that can be consumed without negative consequences.

The HNEL is then multiplied by 1/100 (a "safety factor" of 100-fold), derived from a 10-fold factor accounting for the extrapolation of human safety conclusions based on testing in animals, and an additional 10-fold for normal variability in genetics and other susceptibilities throughout the human population (Rulis and Levitt 2009). This exposure level, the ADI, is considered to be without potential for adverse health effects in humans over their lifetimes. Again, the statutory standard for "safe" is:

“reasonable certainty of no harm.”

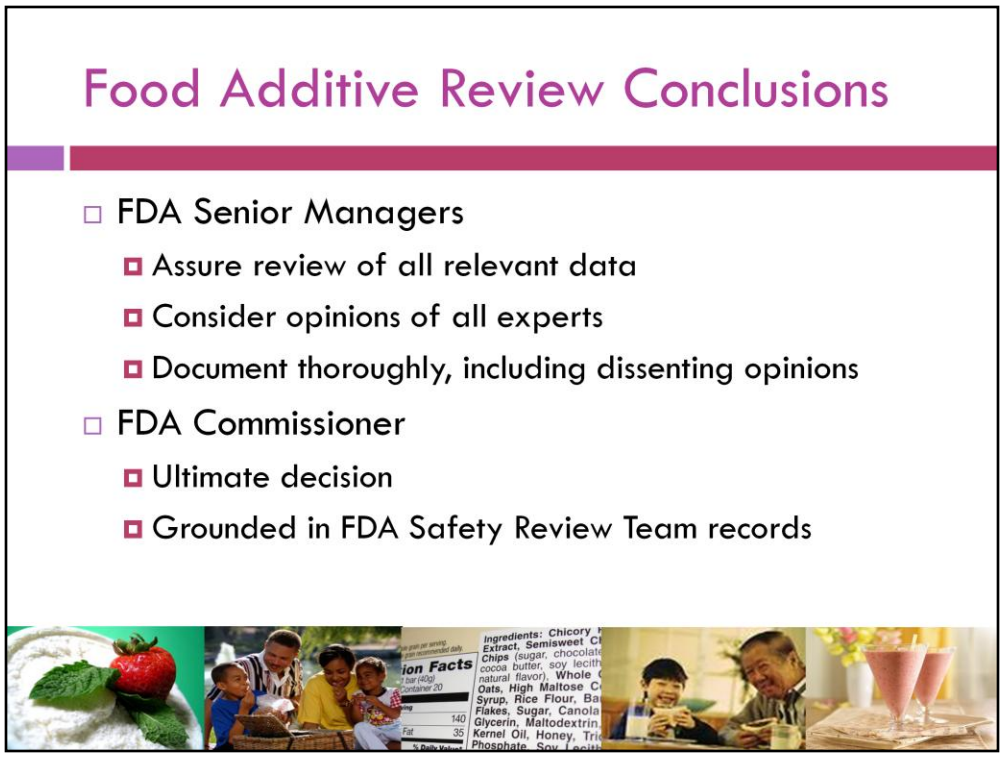
Food Additive Safety Review Process

- The EDI must be lower than the ADI
- When questions remain
  - The FDA may request additional studies
  - Clinical data increasingly necessary with macronutrient replacers

Would the population's expected intake, at the levels expected to be used in the food supply, be safe? To answer this question, the FDA compares the ADI to the EDI (Rulis and Levitt 2009). Although the FDA may use more recently developed techniques for quantitatively assessing risk, the comparison of ADI and EDI is consistently relied upon as an adequate and effective approach for evaluating the safety of an additive.

Even with a favorable ADI/EDI evaluation, questions may remain. FDA may request additional research or data from existing research to clarify issues, such as the fate of metabolites in the gastrointestinal tract, stability of blood glucose levels in people with diabetes ingesting a particular sugar substitute, or unexplained weight gain or loss (Rulis and Levitt 2009).

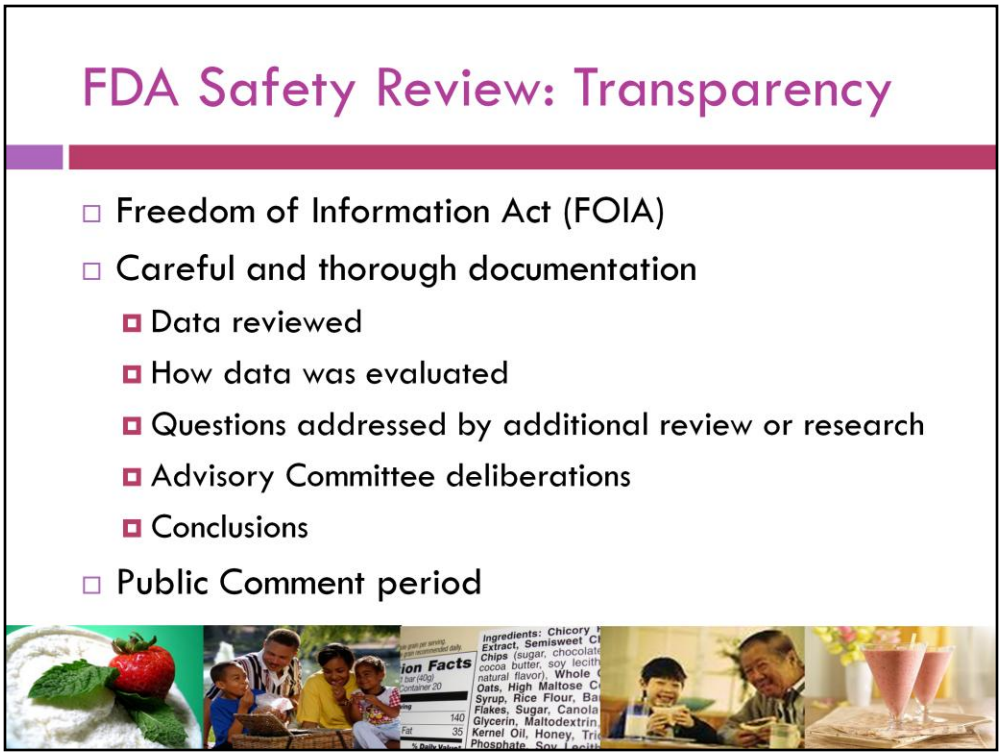
Food additives with the potential to substitute for major caloric components of the diet, such as sugar substitutes (e.g., bulking agents), fat substitutes, or fiber sources, may be ingested in relatively large amounts compared to traditional additives. Therefore, their potential for toxicity in the traditional sense must be quite low, and nontraditional considerations must be taken into account, such as clinical data (Rulis and Levitt 2009). More subtle physiological and nutritional consequences, potential interactions with medications, and potential allergenicity must be resolved. FDA will often involve medical doctors to review data gathered in the clinical setting. This expansion of focus in food additive safety evaluation is becoming the norm.



The conclusions of the FDA safety review team are recorded in the permanent administrative record of the petition (Rulis and Levitt 2009). To ensure the integrity of the process, FDA senior managers are responsible for assuring review of all relevant data, thorough documentation, and consideration of the opinions of all qualified agency experts. Dissenting views must be documented, but not allowed to dominate conclusions of the team.

The ultimate decision about whether to approve a use of a new food additive is delegated to the FDA Commissioner and those working on the Commissioner's behalf (Rulis and Levitt 2009). The Commissioner's decision must be grounded in the administrative record assembled by the FDA safety review team.

If the agency decides to approve the use of the additive, the review team drafts the final rule that is the authorizing regulation, specifying the details of approved use of the food additive (Rulis and Levitt 2009). Formal rulemaking provides the public the opportunity to object, supported by scientific data, and to request a hearing.



Even during the review process, certain pieces of information (especially toxicological studies that are under review) must be released by FDA upon the request of interested parties under the Freedom of Information Act (FOIA) (Rulis and Levitt 2009). FOIA does not require that the FDA release its internal evaluations prior to the publication of its decision regarding a food additive.

The conclusions of the FDA safety review team are recorded in the permanent administrative record of the petition (Rulis and Levitt 2009). Specific details, including the data that was reviewed, how it was evaluated, questions that arose and how they were addressed, and even transcripts of advisory committee meetings, are recorded. This thorough approach is required for transparency, as well as for addressing questions that may arise subsequent to the FDA's approval decision.

Post-Approval

- Post-approval administrative procedures
- Post-approval hearings
- Citizen Petition

Usually, FDA decisions regarding the safety of a new use of a food additive are not challenged. However, several mechanisms are in place to allow for monitoring and debate after the approval decision has been made (Rulis and Levitt 2009). For example, for a short period of time, post-approval procedures and hearings may be pursued by members of the public who object to the FDA's decision and the resulting law. Long-term, anyone may submit a Citizen Petition challenging any regulation.

If an ingredient meets the definition of a food additive, but a company believes there is a consensus of safety that is evident in the public domain, the company may file a GRAS Notice (Rulis and Levitt 2009). The evidence regarding safety for a GRAS Notice must be characterized as follows.

- Supportive of safety for intended use, just as required for a food additive
- In addition, the safety of a GRAS food ingredient must be widely known, such as through:
  - Publication in a peer-reviewed scientific journal
  - Publication of data and information in the secondary scientific literature, such as scientific review articles, textbooks, and/or compendia
  - Availability of unpublished studies (only as corroboration of published scientific findings)
  - Common presence in normal bodily fluids or nature, and a well-known biochemistry
- Safety of the GRAS food ingredient must also be recognized and accepted among qualified experts, as evidenced by:
  - Documentation of "expert panel" opinion
  - Opinion or recommendation of authoritative body, such as National Academies of Science (NAS)
  - Consensus, NOT necessarily unanimous; difference of opinion must be fully addressed

For the sweetener, stevia, for example, the *Stevia rebaudiana (Bertoni) p*lant is native to South America, and has been used for centuries as a natural sweetener. At the time that FDA considered whether stevia met the above standards to be considered GRAS, extracts were already permitted in foods in several other countries. In Japan, in fact, it accounted for 40 percent of the sweetener market. Several GRAS notices have been filed for various steviol glycosides, most of which have been resolved by FDA with no questions, while a few are still pending.

GRAS Notification Evaluation Outcomes

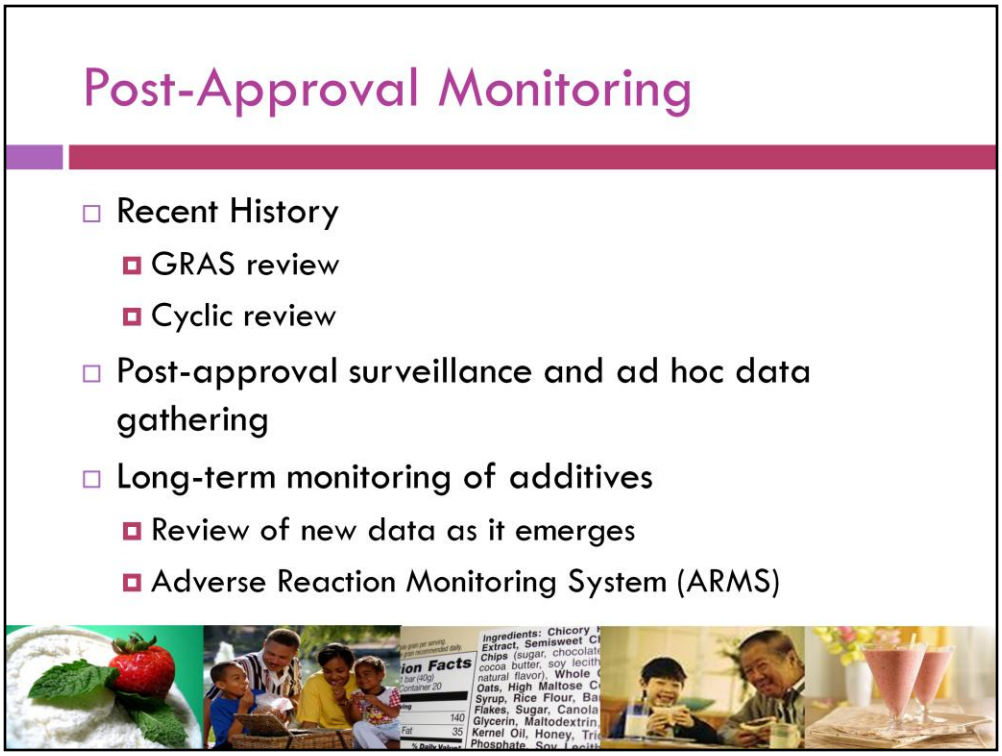
- GRAS determination / No questions / No objections
  - Summarizes data
  - "No questions at this time"
  - "Not made its own determination"
- Notice does not provide basis for GRAS determination
- FDA Ceases Evaluation at Notifier's Request

After the FDA receives a voluntary GRAS Notice, three basic outcomes may result (Rulis and Levitt 2009):

If the notice is found to be in order, the FDA may respond with a summary of the data relied upon by the notifier, state that the agency has "no objections" or "no questions at this time about [the notifier's] conclusions that the material is GRAS under the intended conditions use," and state that the agency has, "not made its own determination regarding the GRAS status of the subject use." The GRAS response language is used to appropriately communicate that the notifier bears the burden of proof, and that the agency does not ''approve" a GRAS notice (ie, a GRAS ingredient should not be referred to as FDA-approved). Still, a "no questions" response is issued by the FDA only when the evidence satisfies the "reasonable certainty of no harm" safety standard, is publicly available, and is generally accepted by a consensus among qualified experts.

Controversy and differences of opinion are rarely absent from scientific opinion. Such realities must be addressed in a GRAS notice with specificity, establishing that the implications of points of disagreement, both individually and collectively, pose no credible challenge to the safety of the ingredient (Rulis and Levitt 2009). If questions or points of disagreement are substantial, credible, and go unanswered in the GRAS notice, a case for general awareness and acceptance by qualified expert consensus is likely to be weak.

If a GRAS notice is deficient, the notifier may choose to withdraw it (Rulis and Levitt 2009). The FDA documents recognition of a withdrawal in a public letter. Otherwise, the FDA issues a public letter to the notifier indicating that the notification is not sufficient to allow a GRAS determination, ensuring that its decision is documented and fully transparent.



Beginning in 1969, eleven years after the first list of GRAS ingredients was published, the FDA initiated the "GRAS Review," a systematic review of the safety of those substances (Rulis and Levitt 2009). In 1972, they contracted the Life Sciences Research Office (LSRO) to summarize existing research for all ingredients in the GRAS review and recommend any new limitations on the use of particular GRAS ingredients. The process was ongoing for many years.

A similar review of already approved additives was conducted in the late 1970's, called the "Cyclic Review" (Rulis and Levitt 2009). Actual intake data and all safety-related research conducted since approval was reviewed, and the FDA found no approved additives that were less safe than determined in the original approval process.

Today, the FDA utilizes different approaches to monitor food additive safety after approval, depending on the nature of the additive (Rulis and Levitt 2009). Because of the ethical necessity of conducting safety testing in animals and the need to estimate human dietary intake prior to actual availability to the public, the FDA may decide that a new food additive should be monitored to gather data based on actual intake. For example, the FDA may use this approach when the margin between the ADI and EDI is particularly close.

Of course, science is evolutionary, with understanding developing over time. Therefore, long-term post-market surveillance of food additives is conducted by FDA (Rulis and Levitt 2009). The intake patterns of populations may change over time, or certain products may be particularly popular or unpopular, affecting the actual exposure of a population to an additive. Research technologies may be developed that allow new approaches to assessing safety. 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. When new data emerges, the FDA performs its own review of the original data and the protocols of new studies. As with review of the original petition, the FDA reviews all data to meet the same high standard for safety.

Also, FDA established the Adverse Reaction Monitoring System (ARMS) in 1985. Through this system, consumers, health professionals, or food companies can submit complaints about adverse reactions to food additives, which are then investigated by the FDA (Rulis and Levitt 2009).

Case Study: Aspartame

- Food Additive Petition to FDA, 1974
  - Chewing gum and dry foods
  - Data submitted:
    - Laboratory animals
    - Humans:
      - Healthy adults, children, infants
      - Special populations: Lactating women; People with diabetes, obesity, phenylketonuria (PKU)
- FDA Approval
  - ADI = 50 mg/kg body weight/day (ie, 20 cans aspartame-sweetened beverage or 100 sweetener packets each day for 70 kg person)

The intense sweetener, aspartame, provides a case study of not only the food additive petition process, but also the rigor of post-market surveillance.

The original petition was filed with FDA in 1974 for use in dry foods and chewing gum (Rulis and Levitt 2009). The data included in the petition was from studies in both laboratory animals and humans. The human studies included those with healthy adults, infants, and children, as well as those who were obese, those with diabetes, and those with phenylketonuria (PKU). The reason for studies in individuals with PKU was that aspartame is composed in part of phenylalanine.

The FDA approved aspartame for use in dry foods and chewing gum, establishing an ADI of 50 mg per kg body weight per day.

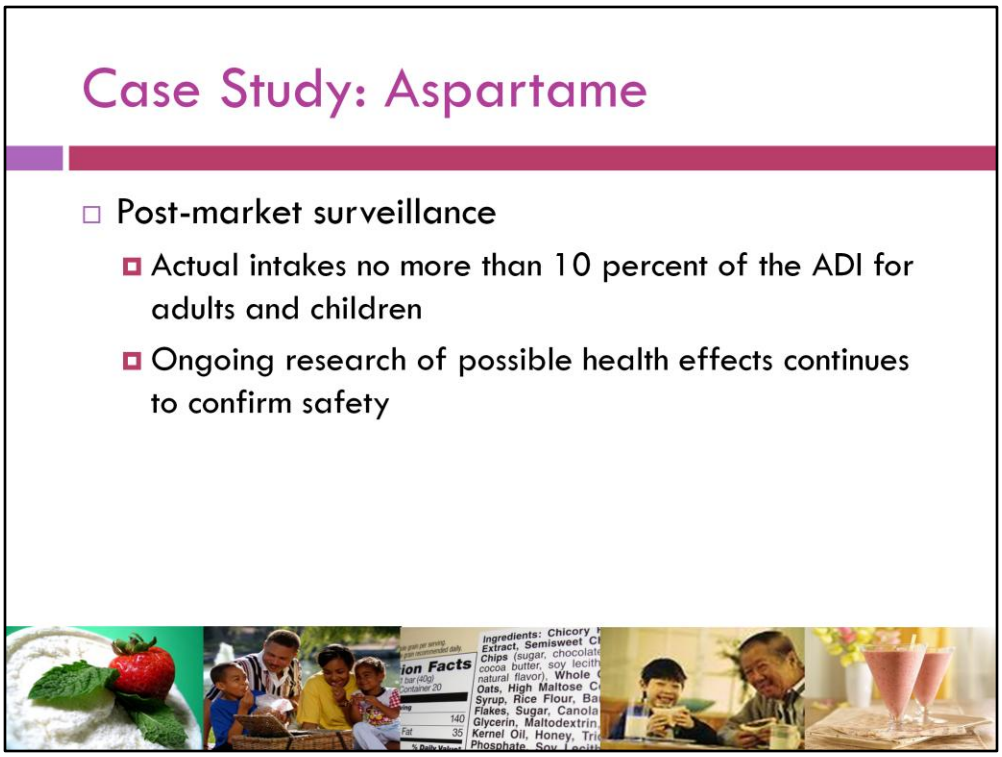
Case Study: Aspartame

- Objections to approval were filed
- FDA stayed approval of aspartame, convened several task forces
- FDA convened Public Board of Inquiry (PBOI)
  - "Split recommendation" (2:1 against approval)
  - Additional animal study submitted, resolved PBOI concern
  - Decision reviewed and reversed by Commissioner
- Approval reinstated 1981, general purpose in 1996

Objections were filed to its approval, leading to FDA's decision to stay the approval of aspartame (Rulis and Levitt 2009). The Agency convened several task forces and a Public Board of Inquiry (PBOI) to reevaluate the data. The PBOI delivered a "split recommendation" (2:1 against approval) in 1981. Subsequently, the petitioner submitted an animal study that addressed the PBOI's concern.

The Commissioner weighed the PBOI decision, as well as the recommendations of the Bureau of Foods (now CFSAN), the animal study data submitted by the petitioner after the PBOI decision (Rulis and Levitt 2009). The Commissioner issued his decision in 1981, stating that the new study resolved the PBOI concern. He stated, ''Few compounds have withstood such detailed testing and repeated close scrutiny, and the process through which aspartame has gone should provide the public with additional confidence of its safety" (FDA, 1981).

Aspartame approval for use in dry foods and chewing gum was therefore reinstated in 1981, and subsequently expanded for use in soft drinks in 1983 (FDA, 1984), and as a general purpose sweetener in 1996 (FDA, 1996).



At the time of its approval for use in soft drinks, the petitioner agreed with the FDA that it would gather data on actual aspartame intake levels to help confirm that it did not exceed the ADI (Rulis and Levitt 2009). The survey was conducted from 1984 to 1994 (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). Based on these data, FDA confirmed that actual consumer exposure was lower than originally projected (EDI), and were much lower than the ADI (Rulis and Levitt, 2009; Vogt, 1995). Specifically, the 90th percentile of consumers, including children, is between 5% and 10% of the ADI, meaning that 9 out of 10 people consume less than 10% of the ADI (http://www.aspartame.org/aspartame_faq.html).

Because of their smaller size, children consume proportionately larger amounts of all food ingredients than do adults in relation to their body weight. The 90th percentile aspartame consumption by children between the ages of two and five is only about 10% of the ADI (http://www.aspartame.org/aspartame_faq.html). Of course, children need calories to achieve proper growth and development, therefore parents, caregivers, and health professionals should work together to ensure that children's diets are calorically and nutritionally appropriate.

In summary, ongoing research of possible health effects continues to affirm the safety of aspartame.

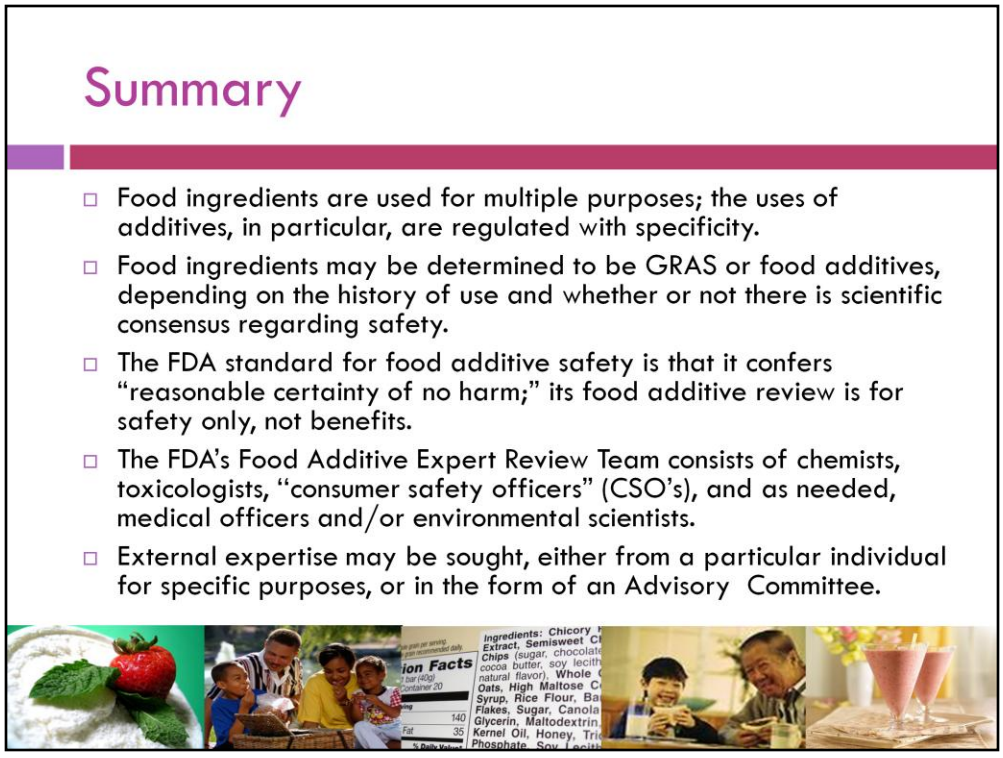
Case Study: Aspartame

- Ongoing research into potential health effects of aspartame and its metabolites
- Adverse Reaction Monitoring System (ARMS)

Complaints about aspartame have been submitted to the FDA via the ARMS (see slide 22). Although the complaint information has not been sufficient to allow FDA to evaluate cause and effect relationships, they have informed further research (Rulis and Levitt 2009). The research has produced no evidence to justify a change in the regulatory status of aspartame. Topics explored include:

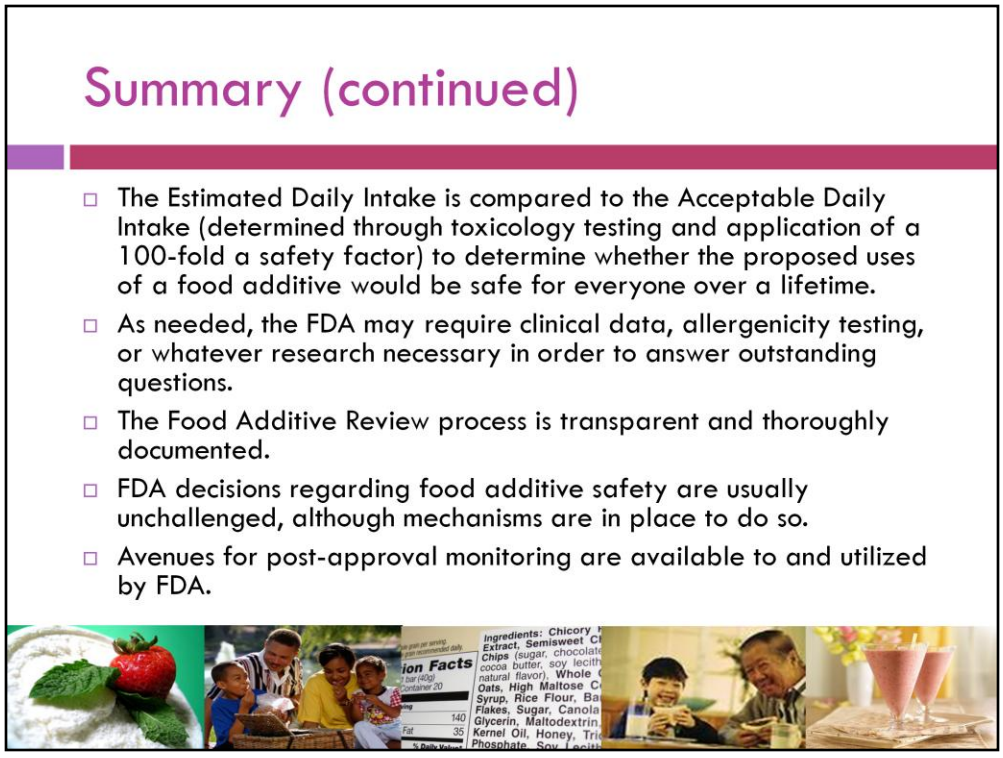
- aspartame and headaches, seizures, behavior, cognition, and mood, allergic-type reactions, and brain tumors;
- the safety of aspartame when consumed by potentially sensitive subpopulations (i.e., individuals heterozygous for phenylketonuria, or with Parkinson's disease, dizziness, depression, liver disease, or renal disease);
- aspartame and the endocrine system.

An extensive review of the full body of evidence on aspartame and health was published in 2007, concluding that the expansive body of evidence on aspartame supports its safety (Magnuson, et al, 2007). In addition, the ADA Evidence Analysis Library has published a review of the data, concluding that strong evidence has demonstrated a lack of adverse effects related to aspartame consumption in the general population, and that evidence, though limited, does not suggest adverse effects for several special populations.



In summary:

- Food ingredients are used for multiple purposes; the uses of additives, in particular, are regulated with specificity.
- Food ingredients may be determined to be GRAS or food additives, depending on the history of use and whether or not there is scientific consensus regarding safety.
- The FDA standard for food additive safety is that it confers "reasonable certainty of no harm;" its food additive review is for safety only, not benefits.
- The FDA's Food Additive Expert Review Team consists of chemists, toxicologists, "consumer safety officers" (CSO's), and as needed, medical officers and/or environmental scientists.
- External expertise may be sought, either from a particular individual for specific purposes, or in the form of an Advisory Committee.



- The Estimated Daily Intake is compared to the Acceptable Daily Intake (determined through toxicology testing and application of a 100-fold a safety factor) to determine whether the proposed uses of a food additive would be safe for everyone over a lifetime.
- As needed, the FDA may require clinical data, allergenicity testing, or whatever research necessary in order to answer outstanding questions.
- The Food Additive Review process is transparent and thoroughly documented.
- FDA decisions regarding food additive safety are usually unchallenged, although mechanisms are in place to do so.
- Avenues for post-approval monitoring are available to and currently utilized by FDA to ensure that emerging evidence is taken into account to ensure safety of additives used in the food supply.

The RD…The Food Safety Expert

- Put food additive safety review knowledge to work
  - Assist patients and clients in making appropriate food choices.
  - Provide education to other health professionals.
  - Be prepared to provide clinical expertise to regulatory authorities.
- For additional resources and the latest updates, visit www.fda.gov/Food/FoodIngredientsPackaging/default.htm.

Consumers, as well as other health professionals, look to the Registered Dietitian (RD) for assurance of safety, or any red flags of caution that are warranted by scientific evidence. Further, the RD may be called upon to serve in an advisory capacity as the FDA considers clinical data in its safety evaluations. To those ends, a thorough understanding of the FDA's process for reviewing new food additives and GRAS ingredients for safety is important foundational information for dietetic professionals. Further reading on this subject is available in the Reference List.

Thank You!

- Complete the Learning Assessment Quiz and check the Answer Key to evaluate your understanding of the material in this module.
- Print the Certificate of Completion and retain for your records.
- Record completion of the module in your Learning Plan.
- Complete the Program Evaluation so that Calorie Control Council may continually improve its CPE offerings.

Thank you for completing this one-hour continuing professional education module on food additive safety regulations. In order to receive CPE credit:

- Complete the Learning Assessment Quiz and check the Answer Key to evaluate your understanding of the material in this module.
- Print the Certificate of Completion and retain for your records.
- Record completion of the module in your Learning Plan.
- Complete the Program Evaluation so that Calorie Control Council may continually improve its CPE offerings.

Visit http://www.caloriecontrol.org/ frequently to learn about other resources for your practice.

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