Appendixes

Appendix A
The Food Additive Approval Process: A Case Study

The primary responsibility of the Food and Drug Administration (FDA) is to ensure that the food and drugs Americans consume and the medical devices and cosmetics they use are safe. In so doing, it ties not to deny or delay unnecessarily Americans' access to new or more affordable foods, food additives, and therapeutics. To illustrate how FDA's review procedures work, this case study discusses the approval process for aspartame, a food additive for which questions about possible neurotoxic effects were raised.

Aspartame, more commonly known as Nutrasweet, is an artificial sweetener that is used by more than 100 million people (3). Users include persons with a medical need to reduce sugar intake, such as diabetics and obese individuals, as well as the general population. The sweetener is composed of phenylalanine and aspartic acid, two naturally occurring amino acids. Aspartame's extreme sweetness, 180 to 200 times that of sugar, was discovered serendipitously in 1965 by two G.D. Searle Corp. scientists, 8 years before submission of the first food additive petition for the compound, After aspartame's approval as an additive, the amount added to foods increased substantially each year until 1985, when it appeared to reach a plateau. Approximately 75 percent of all the aspartame used in the United States is used in carbonated diet beverages. An ongoing dietary survey of aspartame ingestion undertaken by FDA indicates that 35 percent of the population (40 percent of adults) are regular users of aspartame.

The Application Process

preapplication

The first step in the food additive approval process, an informal meeting with FDA staff, is optional. The staff of the Center for Food Safety and Applied Nutrition (CFSAN) encourage applicants to discuss with them the nature of the compound, available animal toxicity data and uses for which approval is sought before formally submitting a petition. In these meetings, potential problems can be identified, enabling applicants to begin any necessary research quickly. Although both CFSAN and the Center for Drugs and Biologics encourage these meetings, they occur much more frequently with drug-licensing applications, where problems are often more evident. G.D. Searle did meet informally with CFSAN staff before submitting its petition in February 1973.

Application

Searle petitioned FDA for permission to market aspartame as an additive for certain foods (38 FR 5921). Section 409 of the Federal Food, Drug, and Cosmetic Act requires FDA to evaluate and act on petitions for approval of food additives. Petitions are evaluated for toxicology, chemistry, probable consumption levels, and potential environmental and health impact. The applicable safety standard is the "reasonable certainty of no harm, " and the burden of proof is on the petitioner. This standard is less stringent than that for new drugs, which must be proven ''safe and effective" in human studies.

The Act does not require specific tests to measure the neurotoxic potential of any compound, and FDA generally assumes that adverse neurobehavioral effects will become apparent during routine toxicological studies in animals. However, if neurotoxic potential is suspected because a substance is structurally similar to a known neurotoxic substance or for any other reason, FDA may specifically require a neurotoxicological evaluation. Normally, only animal toxicity (preclinical) studies are required for foods and food additives. In contrast, new drug approval requires that the results from three phases of human studies be submitted for review.

Review

Following receipt of a petition, FDA personnel identify the types of reviews appropriate for the particular application. Reviews are frequently solicited from FDA staff in other divisions with relevant expertise.

Every application is reviewed for potential toxicity. The ancient Roman credo "moderation in all things" is the first principle of toxicology. Virtually every food and chemical in existence can be toxic in excessive quantities; therefore, the first step is to assess the chemical to which humans will be exposed and estimate the degree of exposure. This is done by testing what happens when the food additive is administered to laboratory-grown mammalian cell lines and animals and by analyzing the chemistry of the compound, including identifying the additive and products of its metabolic breakdown and estimating the likely level of human exposure. These studies identify the types of toxicity caused by the compound and determine the amounts required to produce the toxic effects.

Initially, concerns were raised that aspartame might lead to significantly higher concentrations of phenylalanine in the blood, which could lead to mental retardation in children with the genetic disease phenylketonuria (PKU). One in every 50 to 70 Americans carries the gene for PKU, and every year 200 children are born with this disease (1 of every 14,000 to 15,000 live births). PKU results only if a child has two copies of the gene, one from each parent. Fortunately, if PKU is identified at birth, mental retardation can be prevented by a diet that is restricted in phenylalanine. By law, all newborn babies in the United States must be tested for PKU.

Approval

Toxicological studies on animal models were determined to be sufficient, and Searle's petition to add aspartame to some foods was approved on July 26, 1974 (39 FR 27317-27319). It was approved for consumer use as a dry sugar substitute in granular and tablet form and for industry use as an addition to cold breakfast cereals, chewing gum, and dry bases for beverages, instant coffee and tea, gelatins, puddings, fillings, and nondairy toppings.

The toxicity research on which approval was based included 2-year feeding studies in rats and dogs as well as a lifetime feeding study in rats first exposed to aspartame as fetuses. Based on these studies, a no observed effect level (NOEL), or the largest amount of the additive that could be administered without evidence of toxicity in animals, was established-namely, 2 grams of aspartame per kilogram of body weight. The acceptable daily intake for humans is somewhat arbitrarily set at 100 times less than the NOEL for animals, thus the acceptable daily intake was set at 50 milligrams of aspartame per kilogram of body weight per day. For a 140-pound man, this is the equivalent of approximately 17 (12-ounce) diet sodas or 100 packets of coffee sweetener per day (4). Estimates of the probable maximum daily intake (1.3 to 1.7 grams) were sufficiently close to the acceptable daily intake to permit product approval. The petitioner submitted data from clinical (human) studies which showed that the approved levels of aspartame would not elevate concentrations of phenylalanine in the blood.

Appeal

Two parties objected to the approval of aspartame on grounds of questionable safety and, as is their right, requested a hearing before a judge. However, because of the scientific controversy surrounding the approval process, FDA decided instead to convene a Public Board of Inquiry (15). The board, consisting of three experts appointed by the FDA Commissioner, would hear evidence and make a recommendation to the Commissioner, who would then make the final decision. The board was asked to consider whether aspartame, alone or in combination with glutamate, an amino acid found in monosodium glutamate (MSG), could contribute to brain damage or mental retardation. In addition, if marketing approval were recommended, the board was to suggest appropriate labeling and use restrictions. In response to an additional objection, the board also evaluated evidence that aspartame ingestion resulted in cancer in rats. (The Delaney clause prohibits approval of any food or additive that is shown to be carcinogenic in animals following appropriate testing. If carcinogenic potential is demonstrated, the clause mandates that no level of usage for humans can be considered reasonably safe.)

Before the Public Board of Inquiry was convened, Searle voluntarily suspended plans to market aspartame, pending the resolution of an additional objection, a question about the role of diketopiperazine (DKP, a product of the metabolic breakdown of aspartame) in the development of benign growths in the uterus of female rats (5). (The eventual conclusion was that DKP did not promote the development of these benign growths.) An additional complication resulted from questions raised about the reliability of the animal testing data submitted by the petitioner. As a result, FDA stayed the approval, pending additional review and audit of the animal studies (40 FR 56907). The audit was performed both by the FDA and an independent organization, Universities Associated for Research and Education in Pathology. The process took more than a year and resulted in the conclusion that there were no discrepancies sufficiently significant to compromise the results of the studies.

This conclusion cleared the way for convening the Public Board of Inquiry in January 1980. The board was composed of three distinguished scientists with expertise in neurology, pathology, and nutrition. The role of this board, like other FDA advisory committees, was merely advisory; its conclusions were not binding on FDA, which has statutory responsibility for approval decisions. Solicitation of outside expert opinion, a regular procedure in the evaluation of drugs and biologics, occurs less often in CFSAN. This is presumably because most of their decisions are not controversial. In fact, this board was the first external advisory panel convened by CFSAN.

The panel heard 3 days of testimony, including new clinical data, from FDA staff, G.D. Searle staff, and interested scientists. To the consternation of both FDA and Searle staff, the board's report was not delivered until the fall of 1980. The new clinical data that were presented allowed the board to establish an estimate of the maximum daily intake of aspartame (34 milligrams) by an average-sized man. This step was essential for an evaluation of the toxic potential of aspartame use. The data also demonstrated that the ingestion of very large quantities of aspartame, equivalent to 12 liters of aspartame-sweetened beverage in a single sitting, raised phenylalanine concentrations in the blood to only slightly above normal [from the normal 6 to 12 micromole per deciliter of blood (uM/dl) to 20 uM/dl]. Studies of people with PKU have shown that only sustained, extremely elevated concentrations (above 100 uM/dl, or 50 uM/dl for pregnant women) are associated with developmental brain damage. This damage can be prevented by restricting dietary phenylalanine. **Therefore the board concluded, and FDA concurred, that aspartame use would not contribute to the type of brain damage associated with sustained high levels of phenylalanine in the blood. However, the board did recommend that all aspartame-containing products carry informational**

statements to alert people on phenylalanine-restricted diets.

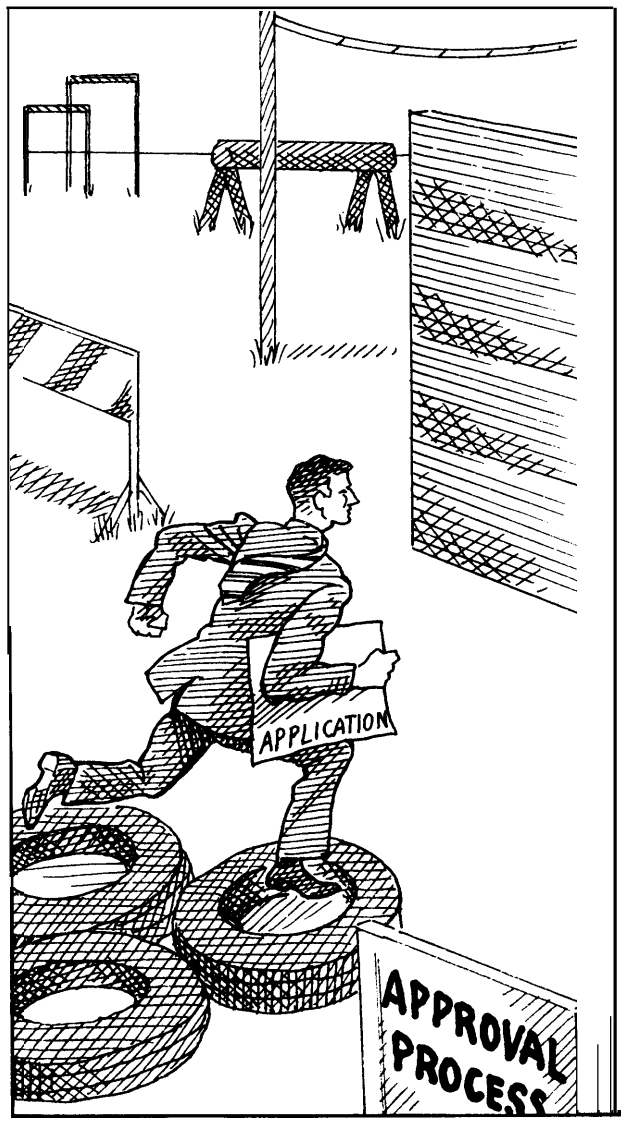
Additional animal and clinical studies demonstrated that the products resulting from the metabolic breakdown of aspartame, alone or in combination with other dietary compounds, including glutamate, had no neurotoxic potential. Clinical studies **of possible toxicity are almost never required for the approval of foods or food additives. The aspartame application was unusual in that the sponsor voluntarily conducted clinical studies and submitted the results to** FDA during the review process. Indeed, ''extensive clinical safety studies were conducted under the (original) food additive petition with the awareness and encouragement of the FDA" in various populations with metabolic disorders (17). The resolution of questions of clinical toxicity requires that clinical studies be carried out, so these would presumably have been required by FDA even if they had not been provided by the sponsor.

The board also found, however, some questions about whether aspartame caused tumors in rats. This finding was based on an incidence of brain tumors, equivalent in the aspartame-treated and control rats, that was higher than the expected incidence of spontaneous tumors. This conclusion would result in automatic disapproval of the food additive petition, as required by the Delaney clause. FDA disputed the validity of the data and cited wide variations in the literature regarding spontaneous incidence of brain tumors in rats, as well as the lack of a statistically significant difference between the treated and control groups.

Final Approval

A decision on the merits of the aspartame application was further delayed to allow all interested parties to prepare exceptions to the findings of the board. In early March 1981, a number of FDA staff members were selected to serve as advisors to the Commissioner for this petition. This group's deliberations were perhaps hurried by Searle's intention to file suit in Federal court against the FDA for unreasonable delay (18). Searle's major concern was that its period of patent exclusivity was being significantly diminished. In 1982, the Senate passed an amendment to the Orphan Drug Act which extended the patent life of products that had experienced unusual regulatory delays in approval.

Following evaluation of additional studies on the question of whether aspartame induces tumors in rats, FDA issued its final ruling in July 1981, a year after the meeting of the board and 8,5 years after the original filing of the petition (see table A-1). The FDA report concluded



Illustrated by: Ray Driver

that there was no evidence that either aspartame or its breakdown product, DKP, contributed to the development of brain tumors in rats. This avoided the obligatory invocation of the Delaney clause,[1] FDA concluded that proper handling of foods containing aspartame would prevent this breakdown and that the consumption of a mishandled product, although possibly unsavory, would be safe.

An additional concern addressed by FDA was that methanol, a metabolize of aspartame, might cause adverse effects. A review of the data revealed that aspartame consumption resulted in the production of smaller amounts

[1] In 1977, FDA, on the basis of convincing evidence of the carcinogenic potential of saccharin in rats, had attempted to remove saccharin from the ''generally recognized as safe' list. The resultant public outcry caused Congress to specifically exempt saccharin from the requirements of the Delaney clause, but at the same time required that foods containing saccharin carry a prominent warning label (8).

Table A-l-Chronology of the Aspartame Petition Process

Date	Action
February 1973	Petition filed
July 1974	Petition approved
April 1975	Searle voluntarily suspends plans to market a response to objections
December 1975	FDA stay of approval to review and authenticate data
September 1976	Data audit initiated
December 1978	Data found acceptable
June 1979	Notice of public hearing
January 1980	Public Board of Inquiry covered
October 1980	Board report represented to FDA
January 1981	Deadline for comments on Board report
March 1981	FDA advisors to Commissioner selected
July 1981	Petition approved

SOURCE: Office of Technology Assessment, 1990.

of methanol than resulted from eating many fruits and vegetables and that this toxic potential was therefore negligible. A final concern was that aspartame, eaten alone or in combination with carbohydrates, might alter the activity of neurotransmitters. A study of infant monkeys fed large quantities of aspartame or phenylalanine continually for 9 months showed that their development and behavior were normal and that there was no evidence of seizures or irregularities in brain waves (1 1). Therefore, aspartame was finally approved as a food additive in July 1981 (46 FR 38285-38308; 40 FR 46394) and for use in carbonated beverages in July 1983 (48 FR 31376-31382).

In the case of aspartame, approval was **based on a massive amount of data derived from animal and human studies. However, the vast majority of food additive petitions are approved on the basis of animal studies alone. It has been repeatedly demonstrated that the effects of active chemicals in animals are not always predictive of their effects in humans.**

FDA has supported limited research on the development of neurobehavioral testing methods to assess potential neurotoxic effects of food additives. Indeed, a 1983 article written by FDA staff concludes with the statement:

> Within the general field of toxicological testing, the FDA Bureau of Foods views the development of behavioral teratological or neurotoxicological testing as one of the most important and urgent areas for future improvement. We await with keen interest the creation of testing paradigms that can be recommended for routine measurement of the neurotoxic potential of food additive substances (5).

Postmarketing Surveillance

Until recently, there was no formal **postmarketing, or Phase** IV, procedure for evaluating any adverse reactions to a newly approved food additive; however, aspartame's approval agreement of 1981 included the establishment of a postmarketing survey. The survey had two components: 1) a poundage survey, in which sales of aspartame to food and pharmaceutical industries were reported; and 2) a dietary survey, in which actual ingestion of aspartame by a sample population was reported. Partially in response to the publicity surrounding the approval of aspartame, FDA also established a passive system of review of consumer complaints. In 1985, FDA asked the Centers for Disease Control (CDC) to evaluate the complaints received. The CDC concluded, on the basis of interviews conducted with 517 complainants, that "although it may be that certain individuals have an unusual sensitivity to the product, these data do not provide evidence for the existence of serious, widespread, adverse health consequences attendant to the use of aspartame" (2).

A more extensive postmarketing reporting system, the Adverse Reaction Monitoring System, was implemented in July 1985 for all food additives as part of FDA's Plan for Action, Phase I. This monitoring system was strengthened in December 1985 with the publication of a "Request for Reports of Adverse Food Reactions" in the *FDA Drug Bulletin. This* announcement requested that physicians and other health professionals inform CFSAN of any severe, well-documented reactions associated with foods, food additives, or dietary practices. In the FDA Plan for Action, Phase II, announced in 1987, this system was expanded to incorporate data from other government agencies, industry, and professional organizations.

Besides monitoring adverse reactions, FDA conducted research in the postmarketing period on the safety of aspartame. A contract was awarded to Battelle Memorial Institute to evaluate the effects of altered amino acid balances on rodent brain function, with an emphasis on neurotransmitters. Also, FDA transferred funds to the National Institute of Environmental Health Sciences in February 1987 for study of the impact of amino acid imbalances on seizure thresholds and neurobehavioral function in rodents. This study is still under way, but preliminary results demonstrate that large doses of aspartame do not affect the sensory or motor functions, learning and memory, or seizure induction in rats (19). Another interagency agreement transferred funds to the Federal Aviation Administration to study the effects of aspartame on the performance of airplane pilots on a number of complex laboratory-based tests of physical and mental function.

Claims of Adverse Effects

Despite the preclinical evidence of safety, there have been numerous consumer complaints alleging that aspartame use resulted insignificant medical problems, including seizures, severe headaches, tremors, insomnia, dizziness, panic attacks, and moodiness. Many of the patients'

symptoms were reportedly reversed when use of aspartame was discontinued. In many of the anecdotal reports there may have been contributing factors, such as excessive dieting, fluid intake, and caffeine consumption. One study (partially supported by the Nutrasweet Co.) of people who claimed to get headaches following ingestion of aspartame demonstrated no difference in their headaches when they ingested aspartame or a placebo (12). However, another placebo-controlled study (in a very small number of patients) found that there was an association between aspartame ingestion and migraines for some patients (7). To date, these are the only controlled studies of the effects of aspartame on people who claim to be sensitive to it, A recent review of research on aspartame was conducted by the Nutrasweet Co., which concluded that ''available evidence confirms that, other than in individuals with homozygous phenylketonuria, who must consider aspartame as an additional source of phenykdanine, aspartame is a remarkably safe food additive" (l).

It is plausible that there may be a small portion of the population that is vulnerable to neurological side-effects following consumption of aspartame. Other "restaurant syndromes" afflicting subpopulations with unusual sensitivity include susceptibility to caffeine, MSG, red wine, and chocolate (13).

The Council on Scientific Affairs of the American Medical Association, in a report based on members' expertise and the scientific literature, concluded in 1985 that "Available evidence suggests that consumption of aspartame is safe except by individuals with homozygous phenylketonuria or other individuals needing to control their aspartame intake" (2). Similarly, in his November 3, 1987, statement to the Senate Committee on Labor and Human Resources, the FDA Commissioner expressed his confidence that no serious, reproducible adverse reactions can be associated with aspartame use. He added that widespread use of aspartame and the publicity regarding possible adverse effects would have guaranteed their identification had they existed (16). Nonetheless, he committed the FDA to continue the postmarketing monitoring of aspartame and to maintain close communication with aspartame's critics. He agreed that some people may be exquisitely sensitive to aspartame and that some people are allergic to the compound. FDA has the authority to remove substances from approved lists on the basis of new information (5). This occurred in 1970, when cyclamate was removed from the "generally recognized as safe" list.

Summary and Conclusions

Because of the continuing dispute about aspartame's safety (9), FDA's approval procedures have been the subject of careful scrutiny. The General Accounting Office and others have concluded that FDA acted entirely properly and according to established policy during the aspartame approval process, but it is not clear whether the established procedures are optimal, striking the best balance between consumer dietary wishes and public health. Critics argue that the procedures are only minimally sufficient and that products which have not been adequately tested are entering the marketplace.

Some of the safety questions emerged as a result of postmarketing passive surveillance, an activity that is optional for food additives but mandatory for drugs. In fact, this distinction between food additives and drugs is itself arbitrary. The acting director of the Bureau of Drugs recommended in an FDA memorandum (which was not issued) that ''safety evaluations of proposed new sugar substitutes be conducted as Phase I studies under the Investigational New Drug (IND) Regulations" (15), Postmarketing monitoring is nearly impossible unless the presence of additives is clearly noted on the food package. Some critics argue that, even when there are unsubstantiated anecdotal reports of toxicity due to ingestion of a food additive, people who feel they are vulnerable to these toxic effects have a right to know the identity and quantity of the suspect additive, This would allow concerned individuals to monitor their intake and would facilitate the reporting of adverse effects. Clearly, consumers cannot report an adverse effect if they are not aware of what they have ingested. This view is supported by some investigators who contend that ingestion of quantities exceeding the acceptable daily intake is possible in some individuals (such as children) and that increasing rates of consumption could lead to more frequent ingestions exceeding the acceptable daily intake (6,10). On the other hand, the Nutrasweet Co., although not opposing the labeling of all food ingredients, would not agree that sufficient scientific evidence of possible toxicity exists to warrant singling out aspartame for obligatory labeling (14).

The value of postmarketing surveillance for identification of neurotoxic effects has been demonstrated several times with new drugs; therefore, many persons argue that establishment of postmarketing surveillance-at least a passive system—should be required for all new products. Because of the difficulty of identifying and quantifying subtle neurological damage and because of the differences between the nervous systems of humans and other animals, an optimal approval process would require clinical studies.

Appendix A References

1. Butchko, H. H., and Kotsonis, F. N., "Aspartame: Review of Recent Research," *Comments in Toxicology, 1988.*
2. Council on Scientific Affairs, American Medical Association, "Aspartame, Review of Safety Issues," *Journal of the American Medical Association 254:40@* 401, 1985.

3. Dews, P. B., "Summary Report of an International Aspartame Workshop," *Food and Chemical Toxicology 25:549-552, 1987.*
4. Franz, M., "Is It Safe To Consume Aspartame During Pregnancy? A Review," *The Diabetes Educator 12:145-147, 1986.*
5. Hattan, D. G., Henry, S.H., Montgomery, S.B., et al., "Role of the Food and Drug Administration in Regulation of Neuroeffective Food Additives," *Nutrition and the Brain,* R.J. Wurtman and J.J. Wurtman (eds.) (New York, NY: Raven Press, 1983).
6. Janssen, P.J.C.M., and van der Heijden, C. A., "Aspartame: Review of Recent Environmental and Observational Data," *Toxicology 50:1-26, 1988.*
7. Koehler, S. M., and Glares, A., "The Effect of Aspartame on Migraine Headache," *Headache 28:10-*13, 1988.
8. Lecos, C., ' 'The Sweet and Sour History of Saccharin Cyclamate , . . Aspartame," *FDA Consumer 15(4):8, 1981.*
9. Maher, T. J,, and Wurtman, R. J., "Possible Neurologic Effects of Aspartame, a Widely Used Food Additive," *Environmental Health Perspectives 75:53-57, 1987.*
10. Partridge, W. M., "Potential Effects of the Dipeptide Sweetener Aspartame on the Brain," *Nutrition and the Brain,* R.J, Wurtman and J,J. Wurtman (eds.) (New York, NY: Raven Press, 1983), pp. 199-241.
11. Reynolds, W.A., Bauman, A. F., Stegink, L. D., et al., "Developmental Assessment of Infant Macaques Receiving Dietary Aspartame or Phenylalanine," *Aspartame,* L.D. Stegink and L.J. Filer, Jr. (eds.) (New York, NY: Marcel Dekker Press, 1984), pp. 405-423.
12. Schiffinan, S. S., Buckley, C. E., III, Sampson, H. A., et al., ''Aspartame and Susceptibility to Headache, ' New *England Journal of Medicine 317:1181-1185, 1987.*
13. Settipane, G. A., "The Restaurant Syndrome," New *England and Regional Allergy Proceedings 8;39-46, 1987.*
14. Shapiro, R. B., "Statement of Robert B. Shapiro, Chairman of the Board and Chief Executive Office of the Nutrasweet Company, Before the Committee on Labor and Human Resources, ' *Nutrasweet Health and Safety Concerns,* U.S. Senate hearing 100-567 (Washington, DC: U.S. Government Printing Office, 1988), pp. 412-423.
15. U.S. Congress, General Accounting Office, *Food and Drug Administration: Food Additive Approval Process Followed for Aspartame,* report to the Honorable Howard M. Metzenbaum, GAO/HRD-87-46 (Washington, DC: 1987), p. **38.**
16. U.S. Congress, Senate, *Nutrasweet Health and Safety Concerns,* hearings before the Committee on Labor and Human Resources, hearing 100-567 (Washington, DC: U.S. Government Printing Office, 1988), p. 227.
17. U.S. Department of Health and Human Services, Public Health Service, Food and Drug Administration, *FDA Medical Review of Clinical Safety Studies,* FAP No. 3A2885, Aug. 20, 1973,
8. U.S. Department of Health and Human Services, Public Health Service, Food and Drug Administration, internal memorandum from the Acting Associate Commissioner for Health Affairs to the Commissioner, Apr. 24, 1981.
9. Young, F. E., "Statement of Frank E. Young, Commissioner, Food and Drug Administration, Before the Committee on Labor and Human Resources," *Nutrasweet-Health and Safety Concerns,* U.S. Senate hearing 100-567 (Washington, DC: U.S. Government Printing Office, 1988), pp. 74-77.