INFANT FORMULA: NATIONAL PROBLEMS

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ISSUE DEFINITION

In the spring of 1982, congressional concern focused for the second time in 3 years on an infant formula that was deficient in a required nutrient. In 1979 infant formulas deficient in chloride (Neo-Mull-Soy and Cho-Free, manufactured by Syntex Laboratories, Inc. of California) had been recalled from the market, following reports of illness among children who consumed the products. Congressional hearings thereafter led to passage of the Infant Formula Act of 1980, which was designed to prevent future problems of deficiencies in these products. The regulations promulgated under this Act had not been finalized, however, when a second incident of infant formula deficiency occurred. On Mar. 3, 1982, the Food and Drug Administration (FDA) and Wyeth Laboratories announced the recall of an infant formula (Nursoy in both concentrated liquid and ready-to-eat forms) that lacked vitamin B6 (pyridoxine). This soy-based product is available for infants who may be allergic to cow's milk formulas. In the week following the Nursoy recall announcement, a second brand of formula, SMA, which is also produced by Wyeth, was recalled. Since these specialized formulas can be the sole source of nourishment for infants, concern has mounted about the possible health consequences of deficiencies. In the vitamin B6 deficiency incident, congressional attention focused on the delay in completing the final regulations for nutrient composition, product testing and recall procedures required under the Infant Formula Act of 1980.

BACKGROUND

Although breastfeeding is the feeding of choice for the human infant, historical records show that mothers have long sought substitutes. These substitutes can be advantageous if the mother is disinclined or unable (either physiologically or psychologically) to breastfeed; the child is unable to breastfeed or has special nutritional needs; or the child is physically separated from the biological mother.

It was not until late in the 19th century, however, that alternative feeding methods started to be fairly safe and reliable. The discovery of the need to pasteurize (heat-treat) cow's milk and modify its composition to be suitable for infant feeding, and the concomitant development of sanitary standards and techniques for milk handling permitted safe bottle feeding. In the late 1800s, milk-based feedings were formulated and prescribed by pediatricians who had begun to study the complex problems of feeding infants. Modern infant formulas evolved from these earlier mixtures.

The composition of infant formula is important since early infancy is the most critical period for growth and development. It is the one time in life that the individual relies on a single product to provide virtually all required nutrients. Progress from the early carbohydrate-modified cow's milk mixtures to formulas closer in nutrient composition to human milk became possible as a result of the advances in overall nutritional knowledge, modern clinical studies that revealed the complexities of infant needs for various nutrients, and technological developments that enabled large-scale production of wholesale formulas with standard composition. When used as directed, these formulas provide protein, fat, carbohydrate, vitamins, minerals and water at the appropriate caloric density and in a form physiologically suited for the infant. Formulas provide an adequate nutritional substitute for

human milk in the support of infant growth and development.

Another major benefit of the development of infant formulas has been the evolution of special formulas for infants with special needs. Dietary problems can include allergy to milk protein, lactose intolerance, gastrointestinal disease and/or diarrhea, low birth weight, or inborn errors of metabolism. Formulas have evolved from carbohydrate-modified evaporated milk products to milk- or whey-based formulas, and most recently, to lactose-free and elemental formulas -- all of which can meet special dietary problems. Lactose-free formulas contain either soy protein, proteinhydrolyzate, or meat base. Other major ingredients include corn syrup solids, sucrose and vegetable oils, as well as all vitamins and minerals known to be essential to the infant. Soy-based formulas were the first of the lactose-free formulas developed for infants intolerant to milk formulas either due to an allergy to milk protein or a temporary deficiency of the enzyme, lactase (which is necessary to break down the sugar, lactose).

According to census data in 1980, there were 3.5 million children aged one year or younger in the United States. Recent data reported on infants at one week of age indicated that in 1980 about 51% received commercially prepared infant formulas compared to 77% receiving formulas in 1971. This change occurred due to a significant increase in the number of mothers who chose to breastfeed their infants. Data on feedings received by infants 5 to 6 months of age indicated that 61% were using commercially prepared formulas in 1980 compared to 28% in 1971. The change in use in this age group primarily represents a shift away from formulas made with evaporated and cow's milk to use of commercial formulas, coupled with some small increase in breastfeeding.

CHLORIDE

Introduction

The 1979 recall of the Neo-Mull-Soy and Cho-Free formulas was a result of inadequate chloride content. Chloride exists in the body almost entirely as the chloride ion. It is primarily located in the extracellular fluid, with a small amount in red blood cells. The ion is important in the regulation of osmotic pressure, water balance, and acid-base balance. Chloride ions are linked to hydrogen ions to provide the acid medium which promotes digestion in the stomach. Chloride is also an activator of saliva, which begins the digestion of food in the mouth.

A minimum daily requirement of chloride has not been determined. However, average intake of sodium chloride (salt) assures that more than adequate amounts are consumed under normal conditions. Most of the chloride ingested comes from salt used in food processing and preparation.

Severe losses or deficiency of chloride can lead to metabolic alkalosis. This condition is characterized by a pH (degree of acidity or alkalinity) of the blood and other body fluids above the normal pH of 7.0. The rise above 7.0 can be due to an excess of alkalies or the withdrawal of acids or chlorides from the blood. Onset of the condition is commonly the result of a loss of acid from excessive vomiting, but also can result from a loss of potassium or ingestion of excessive amounts of sodium bicarbonate. Symptoms and signs include apathy, irritability, delirium, dehydration and occasionally tetany (tonic spasms of muscles). Infants experience a failure

to gain weight, loss of appetite, lethargy and constipation. Treatment includes correction of the primary disorder and administration of sodium or potassium chloride.

Syntex Case

Neo-Mull-Soy and Cho-Free are two brands of infant formula that have been produced by Syntex Laboratories for a decade. At the time of the 1979 recall, it was estimated that these two products represented 10-12% of the infant formula market in the United States and that about 20,000 children were consuming these special products.

In recent years the medical profession, along with consumer groups, has supported the position that the addition of salt in baby foods is not good for the health of children. In 1974 the American Academy of Pediatrics (AAP) recommended that the salt in infant foods, particularly formulas, be reduced to lessen the risk of elevated blood pressure in children. Along with other companies which had modified the salt content of their infant food products, Syntex removed salt (sodium chloride) from Neo-Mull-Soy and Cho-Free in 1978. Coincidental to the removal of salt from the formulas, a decision was made to drop routine chloride assaying of Syntex formulas. The decreased amount of chloride in the formulas caused by the removal of the sodium chloride from the products resulted in metabolic alkalosis in some children fed either of the formulas as their sole source of nourishment.

In July 1979 the manufacturer began to receive reports from doctors of cases of metabolic alkalosis occurring in infants who were using Neo-Mull-Soy. The company notified physicians across the country about the problem with the product. FDA was also apprised of the situation. Late in July, the company convened a panel of experts to review the available data on the reported cases. On Aug. 1, 1979, Syntex decided to recall voluntarily the Neo-Mull-Soy and Cho-Free formulas. Notification of the product recall was sent to physicians and pediatric nurses. The notification included a description of the symptoms of children who had suffered problems, provided information concerning appropriate corrective medical measures, and asked that all cans of the formulas be quarantined. A statement was released to the news media nationwide to alert mothers and other consumers to the recall. Under the procedures of FDA's enforcement policy, the company attempted to retrieve all cans of the product. First, food brokers, wholesalers, retailers and hospitals were notified. Then the company embarked upon a program to conduct checks in order to verify the effectiveness of the recall. The company reportedly contacted almost all of its customers through 26,000 visits made by the company's sales force. In total, over 2 million cans of the formula were destroyed. In the isolated cases where cans were found on store shelves, it was reportedly due to the failure of store owners and middlemen to follow instructions to remove the formula.

Following the incident, Syntex reformulated Neo-Mull-Soy to assure appropriate levels of all ingredients, including chloride. In addition, the company initiated a program to conduct tests for nutrient content on all infant formulas that they manufactured. Finally, the company has supported the follow-up study of all children reported to have had adverse reactions to Neo-Mull-Soy and Cho-Free. This follow-up is being conducted by an independent team of experts.

In a related issue, a nonprofit organization asked Syntex for the formula

deficient in chloride to be donated to their overseas food program. Syntex asked FDA for permission to donate the formula. FDA refused this request on the grounds that formula unfit for U.S. babies would also be unfit for human infants in foreign countries.

VITAMIN B6

Introduction

The 1982 recall of the Nursoy formula was a result if inadequate vitamin B6. Vitamin B6 is not a single substance, but rather a collective term for the naturally-occurring compounds pyridoxine, pyridoxal, and pyridoxamine. The vitamin is essential for cellular function and the proper metabolism of protein and fats. Consequently, the vitamin complex is important for the proper function of the blood, central nervous system (CNS), and skin. The Recommended Dietary Allowance (RDA) of adults is about 2 mg. daily. Primary deficiency is rare in humans since most foods contain the compound. [The best sources are muscle and organ meats, fish, vegetables, and whole grain cereals.] Secondary deficiencies may result in cases of malabsorption, chemical inactivation by drugs, excessive losses, and increased metabolic activity. Experimental deficiency in man leads to clinical evidence of dermatitis, inflammation in the oral cavity, cheilosis (scaling of the lips and angular areas of the mouth), depression, confusion and abnormal electroencephalograms (EEG), followed by convulsions.

For infants under 6 months of age, 0.3 mg. of vitamin B6 daily is considered adequate. The vitamin B6 stores of the normal newborn are sufficient to meet requirements for a month after birth even if the diet is totally devoid of vitamin B6. A daily allowance of 0.6 mg. of vitamin B6 is recommended for the older infant (0.5 to 1 year) consuming a mixed diet. General experience with commercial formulas suggests that metabolic requirements for the vitamin are met if vitamin B6 is present in amounts of 0.15 mg./gm of protein or 0.04 mg./100 kilocalories provided by the formula. In documented cases of vitamin B6 deficiency in infants, the reported cause was either (1) a lack of vitamin supplementation of breastfed infants of poorly nourished mothers, or (2) destruction of the pyridoxine content of infant formula during processing. For infants, dietary deprivation of vitamin B6 may result in epileptic-type convulsions, weight loss, abdominal distress, vomiting and hyperirritability.

Nursoy Case

The lack of vitamin B6 in the Nursoy infant formula was identified by the manufacturer, Wyeth Laboratories. The incident occurred when an employee mistakenly placed a canister of vitamin B1 (thiamin) into a container labeled for vitamin B6. As a result, the batch of defective formula contained no vitamin B6 and too much vitamin B1. The recalled lots of formula were manufactured by Wyeth between Jan. 26 and Feb. 11, 1982. The lots were distributed nationwide and were available for sale in retail stores beginning the first week of February 1982. Initially the recall affected 265,000 13-oz. cans of the concentrated liquid and 306,000 32-oz. cans of the ready-to-use infant formula. However, on Mar. 11, 1982, it was announced that an additional 567,000 cans of SMA brand formula would also need to be recalled. (SMA is a second brand of formula produced by this company). This announcement was followed by a third recall on Mar. 12, 1982, for an

additional 1.8 million cans of SMA. In each case the deficiency of vitamin B6 in the formulas was picked up on routine nutrient analysis, a procedure performed by the company for all batches of the infant formula. The company's batch analysis, however, is performed after the formula has been distributed.

In an earlier case (1952), about 2000 infants, who took another Wyeth formula in which the vitamin B6 had been destroyed inadvertently in processing, had experienced convulsive seizures. Some of these infants have been reported to have suffered permanent brain damage, in the form of cerebral palsy. In the 1982 incident, no actual cases of vitamin B6 deficiency have been reported to date from use of the Nursoy or SMA brands of formula. It is not known in the present case how many infants were fed the defective formula, nor whether any permanent brain damage occurred in those infants who were not yet taking any other foods.

Two additional recalls of nutrient-deficient products have occurred since the Infant Formula Act went into effect in 1980. In August 1983 Loma Linda Foods (Riverside, California) recalled about 274,000 cans of its Soyalac Powder when it was discovered that the formula had a loss of vitamin A activity. In September 1983 Sunrise and Rainbow (Los Angeles) recalled about 7,000 cans and 1,000 packets of its Naturlac Infant Formula Powder when it was determined that the product was deficient in copper, vitamin B6, and thiamine -- that is, the minimum amount required for each nutrient by the Act was not present in the formula when it was analyzed.

LEGISLATIVE ACTIVITIES

Congressional interest in this issue began with reports of the link established between the use of certain baby formulas and the medical disorder, metabolic alkalosis. A hearing was held by the Subcommittee on Oversight and Investigations of the House Committee on Interstate and Foreign Commerce Nov. 1, 1979, to examine the adequacy of the existing law and regulations concerning the manufacture of infant formulas, and the recall procedures when a product is determined to be defective. Following the hearing, several bills were introduced to provide specific provisions for infant formulas in the Federal Food, Drug and Cosmetic Act (FD&C Act), as amended. A number of hearings were held in both the House and Senate to examine the various provisions of the bills. Ultimately, H.R. 6940 became law on Sept. 26, 1980 (P.L. 96-359).

The Infant Formula Act of 1980 created a new section for infant formulas in the FD&C Act, Sec. 412. The term "infant formula" was defined under Sec. 201 (a) to mean "a food which purports to be or is represented for special dietary use solely as a food for infants by reason of its simulation of human milk or its suitability as a complete or partial substitute for human milk". The new provisions established minimum, and where appropriate maximum, levels for nutrient requirements in formula. A formula is deemed to be adulterated if it does not provide nutrients in accordance with levels stated in the law, or if it does not meet the quality control standards for processing. The Secretary is permitted to revise the nutrient requirements, as it becomes necessary.

On an interim basis the Act required the manufacturer to notify the Secretary every 90 days of the nutrient composition of his product until the quality control procedures to be promulgated by the Secretary were in effect.

The final regulations require the manufacturer to notify the Secretary not less than 90 days before the first processing of any infant formula that the formula provides nutrients and meets quality control requirements in accordance with the law. The Secretary is also to be notified of any change in the formulation or processing of a formula to be sure that the product complies with the provisions of the law. In the case where a manufacturer has any knowledge that a formula is not in compliance and presents a risk to human health, the manufacturer has to notify the Secretary.

Under the permanent provisions of the Act, in situations where a recall is required, regulations are to be promulgated to prescribe the scope and extent of recalls necessary and appropriate for the degree of risk to human health presented by the formula subject to the recall. The Secretary is to review the effectiveness of the manufacturer's recall to determine whether it complies with the regulations. Manufacturers are required to keep records on the distribution of their products for use in the event of a recall.

The law exempts from the nutrient and notification requirements any infant formula that is represented and labeled for use by an infant who has an inborn error of metabolism, a low birth weight, or who otherwise has an unusual medical or dietary problem. The Secretary may, by regulation, establish terms and conditions for the exemption of these special infant formula products.

On Mar. 11, 1982, the House Committee on Energy and Commerce's Subcommittee on Oversight and Investigations held a hearing on the rgcall of the Nursoy and SMA formulas. The purpose of the hearing was to determine (1) the circumstances surrounding the vitamin B6 deficiency in the Wyeth products; (2) the status of the FDA regulations concerning infant formula recall and quality control being promulgated as a result of the Infant Formula Act of 1980; and (3) the ability of FDA to carry out the monitoring of such recalls given present budgetary constraints.

Congressional oversight has continued in this area to monitor the effectiveness of the new law and its accompanying regulations in preventing future incidents of defective infant formulas.

REGULATORY ACTIVITIES

On July 26, 1979, the Center for Disease Control (CDC) first began to investigate reports of defective formulas when the agency was notified by local health authorities in Tennessee of three cases of metabolic alkalosis in infants. CDC notified FDA of the reported cases associated with the formulas on the same day. On July 31, 1979, CDC notified FDA that 26 cases of metabolic alkalosis associated with the Syntex products had been identified. By Aug. 31, 1979, there were 115 cases listed in the CDC registry.

On Aug. 1, 1979, Syntex notified FDA of its plans for recall of the products and for public notification. Simultaneously with initiation of the recall, FDA inspected the firm's three manufacturing plants in an effort to determine the cause of the problem and to prevent future problems. Information obtained during the inspections revealed that two formulation changes may have substantially reduced the chloride content of the products: in March 1978 Syntex reduced the sodium content by reducing the salt (sodium chloride); and in June 1978 the soy protein isolate (protein source) was

changed. Another contributing factor may have been a change in the water supply to one of the plants. Inspections also revealed that the firm had

By October 1979 Syntex had reformulated its Neo-Mull-Soy product and planned to begin marketing it. However, FDA asked Syntex to refrain from marketing the modified product until FDA was assured that the newly formulated product was safe and would be manufactured in accordance with accepted nutrient standards and good manufacturing practices.

FDA's recall actions followed the established procedures at that time. However, misinterpretation of recall instructions within FDA caused a delay in monitoring the Syntex recall. In the case of a manufacturer-initiated recall, FDA recall procedures require the agency to confirm the health hazard, evaluate the adequacy of the firm's recall strategy, and classify the recall. The FDA's Health Hazards Evaluation Board rated the Syntex situation as "life-threatening, subacute," meaning that it presented "a significant probability of death" over an extended period of time. The situation was classified as requiring a class 2 recall, based on the opinion that "the risk of death was not immediate and that there would be no irreversible health consequences" if chloride was restored. While FDA's Bureau of Foods intended its instructions to require a 10% level of recall audit to be done by the agency, these instructions were misinterpreted by the FDA San Francisco office to mean that the minimum level of audit requirement was to be undertaken by the manufacturer. When reports revealed that cans of the defective formulas were still on store shelves, the agency notified Syntex of the problem, began its own effectiveness checks, and issued a memorandum to all FDA bureaus and District offices clarifying recall procedures.

As a follow-up to the incident, FDA took several actions. It contacted the manufacturers of all infant formula products to express concern about the recent incident and urged all companies to test their formulas for nutritional composition. FDA also conducted its own tests to determine whether infant formulas currently on the market contained the amounts of the ingredients declared on the label. The National Institute of Child Health and Human Development in cooperation with FDC and CDC, initiated a 5-year follow-up study to assess the long-term health problems associated with use of the two defective Syntex formulas.

Early in 1980 FDA convened two public meetings to discuss various aspects of the infant formula problem. The first was held on Feb. 19-20, to discuss quality assurance and quality control procedures; manufacturing, packaging and labeling; and clinical tests as they relate to infant formulas. The second proceeding on Mar. 12-13 was a public hearing concerned with the possible nutrient composition of infant formulas and possible revisions of existing regulation on infant formulas. Prior to these meetings, FDA contracted with the Federation of American Societies for Experimental Biology (FASEB) to prepare a paper on the various topics related to infant formulas and provide background information for the two public proceedings.

The agency then proposed revision of statutory authority and regulations on infant formulas to require manufacturers to perform certain types of tests and maintain both test records and results to be available to FDA upon request. On Mar. 18, 1980, FDA published in the Federal Register interim guidelines for the nutrient composition and nutrient levels of infant formulas. The recommendations on standards for nutrient levels in infant formulas made by the Committee on Nutrition for the American Academy of Pediatrics (AAP) in 1976 were to be followed by infant formula manufacturers as interim guidelines until revisions in the existing infant formula

regulations were completed. The AAP guidelines for the nutrient composition of infant formulas are based on a consensus of experts on the nutrient requirements of infants and the bioavailability of nutrients from different sources used in infant formulas. (Bioavailability is the degree to which a substance becomes available to the target tissue after administration). During the interim, manufacturers were to notify the Secretary (of DHHS) every 90 days that their formulas were in compliance with the interim guidelines for nutrient standards.

In accordance with the Infant Formula Act of 1980, the proposed regulations for infant formula quality control procedures were published in the Federal Register on Dec. 30, 1980. The comment period, which was to end by Mar. 2, 1981, was extended to May 1, 1981. The final rules, which were published on Apr. 20, 1982, established quality control procedures for the manufacture of infant formulas to assure that formulas contain the necessary nutrients at the levels specified in the Act. The rules require each manufacturer to establish a quality control system, but permits each firm to adopt the system that is best suited to its needs. The final regulations require that an infant formula not be shipped by a manufacturer until the company's own laboratory results establish that certain nutrients are present in the product at the required levels. The previous regulations had allowed an infant formula product to be distributed once the processing was complete without any requirement for testing for nutrient composition. Prior to the Infant Formula Act of 1980, there were no regulatory standards for the nutrient composition of infant formulas, and formulas were regulated under the good manufacturing practices (GMP) regulations applicable to food sanitation and requirements of low-acid canned foods. Under Title 21, new part 106 subpart A of the Code of Federal Regulations (21 CFR 106A) for infant formula quality control procedures, regulations are established for: the status and applicability of the quality control procedures regulation; definitions; ingredients control; in-process control; finished product evaluation; coding; records; and new formulations. The regulations became effective July 20, 1982.

In December 1982, a suit was filed against FDA by several consumer groups who claimed that the FDA's infant formula regulations fail to carry out the mandate of the 1980 law.

In January 1982, FDA proposed regulations for recall procedures to be followed by infant formula manufacturers in accordance with the Infant Formula Act of 1980. These regulations were designed to facilitate the removal of products from the market which do not provide the nutrients required or are otherwise adulterated or misbranded according to the provisions and definitions of the Act. The recall procedures contained in new part 7, subpart d, of 21 CFR specify: the scope and effect, elements, reports, termination, revision, and compliance for a infant formula recall. The final regulations were published in the Federal Register on Apr. 30, 1982, and became effective June 1, 1982, creating specific procedures for infant formulas. Previously infant formulas were recalled under the general enforcement procedures for any food product.

On July 12, 1983, FDA proposed in the Federal Register two additional rules pertaining to infant formula. One proposed rule dealt with exemptions to the Act for specialty formulas intended for use by infants with special medical or dietary needs. Under this regulation, FDA proposed to establish the terms and conditions under which those infant formulas would continue to be exempt. The Act exempted these formulas from requirements set forth in the law until special rules could be promulgated for specialty formulas.

This proposal would also establish quality control, nutrient, and labeling requirements for exempt infant formulas. The second rule, published July 12, was concerned with revising the labeling requirements for infant formula. The proposal would require the label to provide a declaration of nutrients required, expiration date, and directions for preparation and use. This rule, if adopted, will provide necessary information for health care professionals and consumers in the appropriate preparation and use of infant formulas. The comment period for both rules closed Sept. 12, 1983.

On Apr. 11, 1984, FDA published in the Federal Register a proposal to revise the infant formula nutrient requirements of the Infant Formula Act of 1980 to ensure that infant formula products are adequate in meeting the normal infant's total nutritional requirements. The proposed rules would codify most of the nutrients and nutrient levels specified in the Act without change. It would revise the minimum levels for calcium and phosphorus, set maximum levels for iron and iodine, and establish the minimum level for niacin. It would also require that any added vitamin K be in the form of phyllogluinone, the only form of the vitamin permitted in foods. The proposal is based on the recommendations of the Committee on Nutrition of the American Academy of Pediatrics, the Codex Alimentarius Commission's standard for infant formulas, and other sources.

Although the Infant Formula Act of 1980 became law and the regulations promulgated under the statute are in effect, implementation and interpretation of the law remain unclear. Changes in the knowledge of nutrient needs for infants may require frequent modification of nutrient standards in both the law and the regulations. It is unclear at the present time how the law will be interpreted with regard to special formulas classified under the exemption provision and whether the new rules will prevent future incidents of quality control problems with infant formulas.