

# FOOD ADVISORY COMMITTEE MEETING ON INFANT FORMULA

## B1 Briefing Materials

### Overview

Infant formula is defined by law as, in part, a food for use by infants that simulates human milk or is suitable as a complete or partial substitute for human milk. 21 U.S.C. 321(z). For infants who are not fed breast milk, infant formula often serves as the sole source, or the major source, of nutrition during infancy, particularly during the first four to six months of life. During this period of rapid growth and development, nutrient requirements are generally greater than at any other time of life. Without adequate nutrition, infants are unable to achieve the genetic potential for growth and development.

Infant formula is unique in comparison to almost all other foods in that it is often the sole source of nutrition in a rapidly growing and developing vulnerable population. Unlike foods that are included in a mixed diet, nutrient inadequacies in a product that constitutes the only source of nutrition in a diet cannot be compensated for by nutrients in other foods in the diet. Moreover, inadequate nutrition in infancy has the potential to result in serious and irreversible adverse effects. Thus, the importance of proper infant formula manufacture, composition, and nutrient levels cannot be overstated. Senator Metzenbaum, in the legislative history that accompanied the 1986 Amendments to the Infant Formula Act of 1980 explained why infant formula needs more regulation than other foods when he stated “there is simply no margin for error in the production of baby formula. An infant relies on the formula to sustain life and provide the proper nourishment at a time of rapid physical and mental development.”<sup>1</sup>

Since the passage of the 1980 Infant Formula Act and the 1986 amendments, there have been many changes in infant formula products. Advances in scientific knowledge about the composition of human milk and the potential role in infant health and development of various constituents found in human milk have stimulated the addition of new ingredients that serve as new sources of traditional nutrients, or as sources of substances not previously incorporated into infant formulas. New processing and packaging methods have also evolved. Major changes in the formulation or processing of an infant formula cause that infant formula to be considered to be a “new infant formula.”

The purpose of this advisory committee, which includes the *ad hoc* addition of members with expertise in infant nutrition, growth, and development, is to initiate a series of advisory committee meetings to discuss the numerous scientific issues and principles involved in assuring that new infant formulas are nutritionally adequate and support normal physical growth when consumed under their intended conditions of use. This advisory committee will start this discussion by considering scientific principles for

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<sup>1</sup> Congressional Record – Senate S 14042-14047, September 27, 1986.

clinical studies used to evaluate the ability of infant formula products to support normal physical growth in infants. In addition, FDA is asking this Committee to discuss the scientific issues related to the generalization of findings from clinical studies. For example, FDA is asking for a discussion about whether the findings in studies evaluating growth of preterm infants fed preterm formulas can be generalized to term formulas to be marketed for term infants.

Data from premarket clinical studies of infant formulas can be difficult to interpret. For example, test formulas used in clinical studies may not be identical to the formula that is intended for market. Likewise, the infants studied may not be sufficiently similar to the infants for whom a new formula is intended. This raises questions about whether results from one formula can be applied to another formula and whether results from one group of infants can be applied to dissimilar infants who will consume the product. Because of these scientific issues, the agency believes it is appropriate to seek advice of outside experts.

In addition to this Food Advisory Committee meeting, FDA has several other recently completed or newly initiated expert consultations to address other infant formula issues. With respect to ingredient safety, the agency has contracted with the Food and Nutrition Board of the Institute of Medicine (FNB/IOM) to provide recommendations on evaluating the safety of ingredients new to infant formula. Regarding nutrient requirements, FDA contracted with the Life Sciences Research Office to make recommendations on the nutrient requirements for formulas for term and preterm infants. FDA is also awaiting completion of the FNB/IOM's reports on the Dietary Reference Intakes (DRIs) for U.S. population groups. FDA and the National Institute of Child Health and Human Development of the National Institutes of Health (NICHD/NIH) are planning to conduct a workshop to discuss post-market surveillance systems for infant formulas containing new ingredients.

This briefing package provides background information on how infant formula is regulated under the Federal Food, Drug, and Cosmetic Act.

## **Infant Formula Regulation**

### **The Infant Formula Act of 1980**

In 1978, a major manufacturer of infant formula reformulated two of its soy products by discontinuing the addition of salt. This reformulation resulted in infant formula products that contained an inadequate amount of chloride, an essential nutrient for growth and development in infants. By mid-1979, a substantial number of infants had been diagnosed with hypochloremic metabolic alkalosis, a syndrome associated with chloride deficiency. Development of this syndrome in these infants was found to be associated with prolonged exclusive use of chloride-deficient soy formulas.

After reviewing the matter, Congress determined that, to improve protection of infants using infant formula products, greater regulatory control over the formulation and production of infant formula was needed, including modification of industry's and FDA's recall procedures. Accordingly, the Infant Formula Act of 1980 (Pub.L. 96-359) was enacted. This law amended the Federal Food, Drug, and Cosmetic Act to include section 412 (21 U.S.C. 350a). FDA in turn adopted regulations implementing the act, including regulations on recall procedures, quality control procedures, labeling and nutrient requirements.

### **The 1986 Amendments to the Infant Formula Act**

In 1986, Congress revised section 412 of the act to address concerns that had been expressed by Congress and consumers about the 1980 act and FDA's implementation of that statute. These concerns included whether the quality control testing, CGMP, record keeping, and recall requirements that FDA had adopted would prevent children "from ever again being threatened by defective baby formula". The 1986 amendments: (1) State that an infant formula is deemed to be adulterated unless it provides certain required nutrients, meets the quality factor requirements established by the Secretary of Health and Human Services (the Secretary)(and, by delegation, FDA), and is manufactured in accordance with CGMP and quality control procedures established by the Secretary; (2) require that the Secretary issue regulations establishing requirements for quality factors and CGMP, including quality control procedures, (3) require that infant formula manufacturers regularly audit their operations to ensure that those operations comply with CGMP and quality control procedure regulations; (4) expand the circumstances in which manufacturers must make a submission to the agency (manufacturers must do so when making major changes that may affect whether the formula is adulterated); (5) specify the nutrient quality control testing that must be done on each batch of infant formula; (6) modify the infant formula recall requirements; and (7) give the Secretary authority to establish requirements for

retention of records, including records necessary to demonstrate compliance with CGMP and quality control procedures.

In passing the Infant Formula Act of 1980 and the 1986 amendments, Congress created infant formulas as a special class of foods. In the legislative history that accompanied the 1986 amendments, Senator Metzenbaum explained why infant formula needs more regulation than other foods when he stated “there is simply no margin for error in the production of baby formula. An infant relies on the formula to sustain life and provide the proper nourishment at a time of rapid physical and mental development”. In a 1996 proposal, FDA described its thinking on the importance of proper infant formula manufacture, composition, and nutrient levels (61 Fed. Reg. at 36155 (1996)). FDA stated that relative to per unit of body weight, nutrient requirements are generally greater in infancy than at any other time during life. During the first year, the rate of growth is at its maximum, with birth weight typically doubling by 4 months of age and tripling by 1 year. Moreover, the metabolic rate in infants is greater, and the turnover of nutrients is more rapid, than in adults. Thus, infants must ingest adequate nutrients to support a rapid rate of growth and of developmental changes and to supply maintenance needs. Without adequate nutrition, infants would be unable to achieve their genetic potential for growth and development. (61 Fed. Reg. at 36155 (references omitted)).

In the proposal, FDA also stated that these nutritional needs must be met in early infancy by food in liquid form. Sucking and involuntary swallow reflexes are the mechanisms by which very young infants ingest food until teeth and motor coordination develop. Consequently, for infants who are not fed breast milk, infant formula often serves as the sole source, or the major source, of nutrition during this time of rapid growth and development (61 Fed. Reg. at 36155).

### **Definition of Infant Formula**

As noted in the overview, infant formula is defined by law.

Under 21 U.S.C. 321(z), infant formula is defined as:

a food that 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.

In the legislative history of the Infant Formula Act, whenever the words “sole” or “solely” are used, they appear in the context of describing infant formula as the “sole” or primary source of nutrition for infants or babies. For example, in explaining how the 1980 act would change existing laws, then-Congressman Gore stated: “First it would require that any infant formula marketed in the United States as the sole source of nutrition for normal babies include minimum amounts of all essential nutrients” (61 Fed. Reg. at 36156-7). Congressman Mottl stated that the 1980 act “is concerned with human lives

at their most vulnerable stage. We are talking about food that may be the sole source of nourishment for infants.” (61 Fed. Reg. at 36157).

## **Regulatory Requirements**

A number of different activities are involved in regulating the safety and nutritional adequacy of infant formula ingredients and products. Manufacturers or distributors of infant formula to be marketed in the United States must comply with the requirements for foods of the Federal Food, Drug, and Cosmetic Act (the act), 21 USC 321 *et seq.*, and FDA’s implementing regulations, Title 21 of the Code of Federal Regulations. Infant formula must comply with the general food provisions of the act. In addition to the general provisions, Congress established other requirements that are specific to infant formula. An overview of the types of infant formula requirements is briefly described below.

### **General ingredient safety requirements**

Under section 409 and 201(s) of the act, each ingredient added to food, including infant formula, must either be approved for the use as a food additive, or be generally recognized as safe (GRAS) for its intended use. “Safe or safety” means that there is a reasonable certainty in the minds of competent scientists that the substance is not harmful under the intended conditions of use. In addition to the general ingredient safety requirements of the act, Congress established, under section 412 of the act, specific requirements for infant formula that are intended to ensure that infant formula is safe and suitable for its intended use, that is, as a sole source of nutrition to support healthy growth of infants. Recognizing that infant formulas frequently serve as the sole source of nutrition in a stage of life that is critical for growth and development, Congress determined that infant formula needed more regulation than other foods.

### **Requirements specific to infant formula**

Manufacturers must provide FDA with assurances that the requirements specific to infant formula have been met for each “new” infant formula product prior to marketing. A “new infant formula” includes:

- (1) An infant formula manufactured by a person which has not previously manufactured an infant formula, and

(2) An infant formula manufactured by a person that has previously manufactured infant formula and in which there is a major change in processing or formulation from a current or any previous formulation produced by such manufacturer.  
(21 U.S.C. 350a(c)(2).

A “major change” is defined in an infant formula as:

any new formulation, or any change in ingredients or processes where experience or theory would predict a possible significant adverse impact on levels of nutrients or availability of nutrients.

((21 C.F.R. 106.30 (c)(2))

Examples of “new” infant formulas include:

1. Any infant formula produced by a manufacturer who is entering the U.S. market;
2. Any infant formula powder processed and introduced for commercial or charitable distribution by a manufacturer who previously only produced liquids (or vice versa);
3. Any infant formula having a significant revision, addition, or substitution of a macronutrient (i.e., protein, fat, or carbohydrate), with which the manufacturer has not had previous experience;
4. Any infant formula manufactured on a new processing line or in a new plant;
5. Any infant formula manufactured containing a new constituent not listed as a required nutrient under the act, such as taurine or L-carnitine;
6. Any infant formula processed by a manufacturer on new equipment that utilizes a new technology or principle (e.g., a change from terminal sterilization to aseptic processing); and
7. An infant formula for which there has been a fundamental change in the type of packaging used (e.g., changing from metal cans to plastic pouches), as cited in FDA Guidelines Concerning Notification and Testing of Infant Formulas (1986) as cited in 21 U.S.C. 350a(c)(2).

Several types of requirements are specific to infant formula. These include:

- Current good manufacturing practices (CGMP) help ensure that all of the required nutrients and other ingredients are included at designated levels in the formula, and that the formula is not contaminated with microorganisms or other materials that may be harmful to infants. The designated levels of nutrients must be within ranges established by statute and regulation.
- Quality control procedures ensure that the infant formula contains the nutrients that are necessary to support growth and development, at the appropriate levels, not only when it enters into commerce but throughout its shelf life. Under the authority of the act, FDA has promulgated regulations that specify quality control

procedures for assuring nutrient content of infant formulas, records and reports, and submission requirements.

- Nutrient requirements. Section 412(i) of the act includes a table that lists nutrients that every infant formula must contain. This section also establishes a minimum level for each of the listed nutrients and a maximum level for certain of those nutrients. FDA may revise the list by regulation. Currently listed nutrient requirements for infant formulas are found in 21 C.F.R. 107.100.
- Quality factor. This term refers to the nutrient potency and biological effectiveness of a formula, as formulated, e.g., formulas need to be adequate to support normal physical growth. Subsequent processing, ingredient interactions, and time should not reduce biological effectiveness of a formula. Manufacturers need to make sure that unsafe nutrient levels or by-products are not created from ingredient addition or breakdown, or interactions caused by processing or time.

By establishing provisions for CGMP, quality control and quality factors, Congress indicated its intention that infant formulas marketed in the United States should not only be safe, and contain all of the nutrients required to support infant growth and health, but should provide those nutrients in a bioavailable form to ensure that the infant formula will, indeed, support infant growth and health.

Under the act, section 412 (c)(2) requires that the formula will not be marketed unless assurances are provided that quality factor requirements have been met for each “new” infant formula product. Quality factor assurances are thus product specific, rather than generic, in nature.

For each “new” infant formula product (which includes any infant formula that has had a major change in its formulation or processing), FDA evaluates whether a manufacturer has met the quantitative and quality requirements for essential nutrients in a new infant formula to ensure that the infant formula is likely to meet all of the known nutritional needs of infants and whether the formula will provide for normal physical growth when infants consume the formula as the sole source of nutrition.

FDA also monitors illnesses and injuries associated with the use of an infant formula. FDA’s adverse event monitoring system includes the monitoring and evaluating of adverse event reports associated with infant formulas. As warranted, consumer and physician warnings are published, and enforcement actions are taken.

## **Summary**

In passing the 1980 Infant Formula Act and its 1986 amendments, Congress recognized infant formulas as a special category of foods that, because there is no margin for error in ensuring the healthy growth and development of infants, requires more regulation than other types of foods. Regulation of infant formulas involves both general safety

provisions of the act and additional requirements specific to infant formulas (e.g., CGMPs, quality control procedures, nutrient levels and analysis, and quality factors). For most of the requirements specific to infant formula, manufacturers must provide assurances that the requirements have been met for each “new” product (including marketed products in which a major change has occurred) prior to marketing.