



**DECISION TREE FOR DOCUMENTATION OF NUTRITIONAL ADEQUACY
OF A NEW OR CHANGED INFANT FORMULA**

Developed by the U.S Infant Formula Manufacturers
October 21, 2002

For further information: Contact the International Formula Council, 404-252-3663

Decision Tree for Documentation of Nutritional Adequacy of a New or Changed Infant Formula

The Food Advisory Committee (FAC) has been asked by the Food and Drug Administration (FDA) to provide advice and recommendations to the FDA on general scientific principles in assessing and evaluating “new” infant formulas (*Federal Register*, October 16, 2002, Vol. 67, Number 200, 63933). In preparation for the November 18-19 FAC meeting, this document offers (1) background information on the objectives of industry comment to the FAC and industry understanding of FDA regulatory oversight of infant formula, and (2) a decision tree analysis that infant formula manufacturers conduct to ensure a new or changed infant formula is nutritionally adequate.

BACKGROUND

Objectives of Industry Comment to the FAC

- Work with FDA and outside experts to maintain science-based standards for the development of infant formula.
- Ensure that FDA has access to necessary expertise to develop criteria for assessing when clinical studies in infants are necessary and what should be the attributes of any such study.
- Maintain high scientific standards to improve infant formulas with strong science and to ensure protection of this vulnerable population.

Industry Understanding of FDA Regulatory Oversight of Infant Formula

The FDA, acting through several offices in its Center for Food Safety and Applied Nutrition (CFSAN), is actively engaged in assuring that infant formulas comply a) with the wide array of laws designed to assure the safety of all foods in the U.S. food supply; and b) with laws specifically targeted at infant formulas to assure that they are safe and provide appropriate nutrition to substitute for human milk¹

- FDA's Office of Nutritional Products, Labeling and Dietary Supplements (ONPLDS), is principally responsible for assuring that infant formulas meet the stringent requirements established by Congress in the provisions of the Federal Food, Drug, and Cosmetic Act (“FD&C Act”) applicable to infant formulas. (FD&C Act §412). A principal responsibility of ONPLDS's is to confirm manufacturer assurances that a given infant formula, as a whole, (i.e., the matrix), provides the appropriate *nutrition* to substitute for human milk. These assurances are buttressed by ONPLDS' authority to confirm that all infant formulas:
 - Provide the nutrients required by law (FD&C Act §412(i); 21 CFR §107.100)
 - Meet established nutrient quality factor requirements (FD&C Act §412(b)(1))
 - Are manufactured pursuant to established Good Manufacturing Practice and Quality Control requirements (FD&C Act §412(b)2; 21 CFR Part 106)
 - Are appropriately labeled (21 CFR Part 107, Subpart B)

¹ Copies of the portions of the FD&C Act and FDA regulations specifically applicable to infant formula are attached.

- FDA's Office of Food Additive Safety (OFAS) oversees manufacturer assurances that food ingredients are *safe* for their intended use – regardless of whether the intended use is in infant formula or in other foods. (FD&C Act §201(s); 21 CFR Parts 170 and 182)
- The Field Operations of FDA's Office of Regulatory Affairs (ORA) regularly conducts unannounced inspections and audits of infant formula manufacturing facilities, procedures and records to assure compliance with current Good Manufacturing Practices (GMPs) and notifications previously submitted to ONPLDS. (FD&C Act §704)
- An extensive range of documents must be maintained by the manufacturer and provided to FDA when requested, including records documenting thorough investigations of any complaints or adverse events (AEs) reported to any manufacturer. (FD&C Act §412(b)(4); 21 CFR §106.100(k))
- If a manufacturer fails to comply with the laws relating to infant formula, FDA has the power to seize the infant formula, initiate recalls, obtain injunctions against further manufacture and/or pursue criminal prosecution of the manufacturer. (FD&C Act §§412(e); 301(a)-(g),(s), 302, 303 and 304)

In summary, the nature of ONPLDS' regulatory oversight is one of pre-market *review*, not pre-market *approval*. Under the law, the ultimate responsibility and accountability for producing safe and nutritionally adequate infant formula remain solely with the manufacturer.² (FD&C Act §412(c) and (d)).

DECISION TREE ANALYSIS

Please refer to the attached Decision Tree chart as you read the following text.

Extent of Formula Change

A. New Infant Formula

For any formula, process, or package that is wholly new to the manufacturer, the manufacturer is required to provide documentation to ONPLDS, at least 90 days before commercial distribution, that the formula provides appropriate nutrition to substitute for human milk. This documentation, as required by FDA regulations, will include assurances that the formula meets established "quality factors" as appropriate. [FD&C Act §412(d)(1)(C)]

² The Infant Formula Act of 1980 ("IFA") "did not authorize any form of preclearance by the FDA for the marketing of an infant formula." * In 1986, Senator Metzenbaum's bill to amend the IFA contained a provision requiring premarket approval of "new or altered" formulas. However, he subsequently stated "The FDA has since made a strong case that a premarket approval is not desirable in this instance. FDA points out that the burden to produce a safe and effective formula should remain squarely on the shoulders of the manufacturers." Senator Hatch added "I also agree with the FDA that premarket approval is not desirable in this instance and understand that this procedure is not intended to become a precursor of such FDA action." ** This congressional intent remains in place today.

* Report by the Committee on Labor and Human Resources United States Senate, Infant Formula Act of 1980, August 26, 1980. Pages 5 - 6.

**Congressional Record - Senate, September 27, 1986. Pages S14046-7.

B. Infant Formula Change (in ingredients, formulation, processing, packaging, etc.)

1. MINOR CHANGE: "...Where experience or theory would not predict a possible significant adverse impact on nutrient levels or nutrient availability," the manufacturer will provide ONPLDS with notice of the change before first processing. [21 CFR §106.30(c)(1); FD&C Act §412(d)(3)]. The notification will include assurance based on manufacturer's scientific knowledge, experience, and medical theory that the modified formula will remain nutritionally comparable to the currently marketed US formula.

Examples of Minor Changes from the attached FDA Guidelines³

- a. Minor reduction of iron level
 - b. Replacing certain nutrient forms with another form.
 - c. Adjustments in the quantity of a nutrient in a premix or individually added nutrient that results in a specification change for that nutrient in the finished product.
 - d. Changes in time-temperature conditions of preheating during handling of bulk product that cannot reasonably be expected to cause an adverse impact on nutrient levels or nutrient availability.
 - e. Changes in oxygen content of a packaged product that might have a minimal effect on the level of nutrients.
-
2. MAJOR CHANGE: If, however, manufacturer's "experience or theory would predict a possible significant adverse impact on levels of nutrients or bioavailability of nutrients, or any change that causes an infant formula to differ fundamentally in processing or in composition from any previous formulation produced by the manufacturer,"⁴ the manufacturer will provide FDA with notice, 90-days prior to marketing, that includes documentation from which it can be concluded that no significant adverse nutritional impact to the intended infant population will occur as a result of the change to the subject infant formula.

FDA Examples of Major Changes⁴

- Any infant formula produced by a manufacturer who is entering the U.S. market;
- Any infant formula powder processed and introduced for commercial or charitable distribution by a manufacturer who previously only produced liquids (or vice versa);
- 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;

³Guidelines Concerning Notification and Testing of Infant Formulas, August 1, 1986

⁴61 *Federal Register* 36153, 7/9/1996 (Proposed Rule)

- Any infant formula manufactured on a new processing line or in a new plant;
- Any infant formula manufactured containing a new constituent not listed in section 412(i) of the act, such as taurine or L-carnitine;
- 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
- 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).

C. Documentation of Nutritional Adequacy

Documentation of nutritional adequacy can take many forms. Since minor changes do not trigger any expectation of adverse impact on nutrition, they do not require clinical trials. Major changes may or may not require clinical trials. Because of the concerns inherent in any clinical trial in a vulnerable population, reliance on clinical trials should not be routine. Consideration of other sources of documentation should always be the first step. Thus, the manufacturer will provide documentation that may be based on one or more of the following:

- previous experience with the change,
- various types of non-clinical testing, both *in vivo* and *in vitro*,
- internal medical-scientific assessment,
- independent expert review,
- current medical practice,
- published scientific literature,
- published guidelines of authoritative bodies such as AAP/CON, NAS, ADA, ASPEN, and NASPGHAN.

D. Documentation Other than Clinical Studies

1. Documentation of Changes That Do Not Require Clinicals

With any given change, the nature of what constitutes appropriate documentation of continuing nutritional adequacy or comparability to a similar marketed infant formula will depend on the specific nature of the change and the specific basis of the expectation of a possible adverse nutritional impact. The following examples illustrate a few possible changes along with likely methods of assessing there is no change in nutritional adequacy as compared to the manufacturer's previous experience:

<u>Formula Changes</u>	<u>Documentation</u>
Change in packaging type (e.g., changing from metal cans to composite cans or plastic pouches for a powder product).	Stability testing; documentation of safety of food contact surface materials; description of physical characteristics of finished product

Manufacture of an infant formula in a new plant, or complete new production line using substantially similar processing methods.	Validation plan; Verification testing of finished product
Changes in processing (e.g., time/temperature conditions of preheating, handling, mixing, sterilizing of in-process product) where the end conditions are within normal parameters in customary use in making infant formula.	Manufacturer's previous experience and knowledge covering nutrient stability and interactions under such changed conditions; Verification testing of finished product
Changes in product type from liquid to solid or vice versa where the heat treatment differences can be shown to have minimal impact on the protein quality.	Manufacturer's previous experience; demonstration/scientific support of continued biological value of protein; Verification testing of finished product

2. Examples of Changes That Do Not Require Clinicals

a. AAP/CON Examples

In 1988, the American Academy of Pediatrics Committee on Nutrition (AAP/CON) prepared a report, "Clinical Testing of Infant Formulas with Respect to Nutritional Suitability for Term Infants," under contract with the FDA. Although the report did not address major and minor infant formula changes, it did include (on page 23) the following "changes in formulation and processing that will generally not warrant clinical testing:"

- Changes in energy concentration if the final energy concentration is at least 63 kcal/dl and no more than 71 kcal/dl
- Changes in percentages of energy supplied by fat and carbohydrate within the limits specified by the FDA rule
- Changes in the proportions of fat (with the exception noted in the report) provided from various sources
- Changes in the proportions of carbohydrate provided from various sources.
- Changes in protein concentration if the final protein concentration is at least 2 g/100 kcal and does not exceed the limit specified by the FDA rule (currently 4.5 g/100 kcal)
- Changes in proportions of protein supplied by non-fat cow milk and cow milk whey proteins, or changes of less than 10% in the proportion of protein supplied by other sources
- Increases in iron concentration between 0.2 and 1.0 mg/100 kcal or between 1.8 mg/100 kcal and the upper limit permitted by the FDA rule (3.0 mg/100 kcal)
- Changes in vitamin concentrations within the limits specified by the FDA rule

- Removal or addition or changes in the level of a GRAS emulsifier (e.g., carrageenan, mono & diglycerides, lecithin) present at an insignificant level of energy intake (This item was discussed on page 25 of the same report.)

b. Industry Examples

The following examples are proposed for consideration as possible additional changes where nutritional adequacy could be documented without resort to a clinical trial, regardless of whether the change is classified as “major” or “minor”.

- Substitution of one fat source for another, both of which are commonly used and have been well studied in infant formulas, within the range of levels of previous use in infant formula (e.g., substitution of high oleic safflower oil for high oleic sunflower oil, when both fat blends have been documented to perform well in other formulas).
- Addition of minor constituents added for their potential nutrient contribution, but for which there is no reasonable basis to predict that they would materially impact nutritional adequacy (e.g., taurine and L-carnitine).
- Replacing one nutrient form with another where both are known to perform well in infant formulas (e.g., replacing vitamin A acetate with vitamin A palmitate).
- Reductions or increases in nutrient levels that result in final nutrient levels that remain within the requirements of the regulations and that are known to fall within ranges substantially free of significant adverse nutrient interactions.
- Implementation of any recommendation made by a competent scientific body which also reviews and independently considers safety issues.
- The addition of any ingredient that is determined to be GRAS for infant formula, when supported by well-accepted scientific rationale and/or experience in the manufacturer’s formulation, and that raise no reasonable expectations of a significant adverse impact.

E. Documentation with Clinical Studies

If the above forms of assurance would be insufficient to conclude that no significant adverse nutritional impact to the intended infant population will occur, then the documentation should include results of a clinical study in infants. Clinical trials must be scientifically and ethically justified, not unduly invasive, unreliable, or redundant and must be consistent with the principles of 21 CFR 50 and 56. Practical difficulties should also be recognized (e.g., delay of availability of products – particularly for vulnerable populations, and/or scarcity of subjects). Additionally, where clinical trials are necessary, they should include relevant clinical outcomes pertinent to the question of nutritional adequacy. These clinical trials may or may not include growth assessments as an outcome.