QUESTIONS

FOOD ADVISORY COMMITTEE ON INFANT FORMULA
FOOD AND DRUG ADMINISTRATION
November 18-19, 2002

Background

In the Infant Formula Act of 1980 and the 1986 Amendments, Congress provided for the establishment of quality factors, i.e., factors necessary to demonstrate that the infant formula, as prepared for market, provides nutrients in a form that is bioavailable and safe as shown by evidence that demonstrates that the formula supports healthy growth when fed as a sole source of nutrition. In providing for quality factors, Congress recognized a need to ensure that each infant formula product contains an adequate amount of each nutrient in a form that can be digested, absorbed, and utilized to meet the infant's physiological needs.

The Food Advisory Subcommittee is being asked at this meeting to consider two issues.

1. The first issue regards criteria for the adequate evaluation of normal physical growth during the first six months as an indicator of the nutritional adequacy of new infant formulas. Questions for the committee inquire about the types of techniques available to measure physical growth, tools available to evaluate the data (bioequivalence and normative standards), and the usefulness of different types of comparisons. Consideration of these questions should focus on physical growth of term and stable preterm infants consuming formula enterally. (Note: Six months of age means six months corrected age for preterm infants.)

2. The Food Advisory Subcommittee is also being asked to consider the types of changes in infant formulas that should be accompanied by a clinical study assessing normal physical growth in order to provide assurances of safety. Considerations could include, but are not limited to, a) interactions affecting potential bioactivity or bioavailability among individual formula components in an infant formula matrix during formulation, processing, and storage and b) interactions of the matrix components with the absorptive surfaces or milieu of the infant. Table 1 lists examples of changes that can be made to infant formulas, including some potential future changes. This table is intended as a guide, not a definitive list.

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Questions about Evaluation of Normal Physical Growth as an Indicator of the Nutritional Adequacy of New Infant Formulas

The following questions refer to the assessment of normal physical growth of infants from birth to 6 months of age consuming new infant formula:

METRICS FOR THE EVALUATION OF NORMAL PHYSICAL GROWTH

1. What are the values and merits individually, and in combination, of the following metrics for assessing normal physical growth?

   - body weight
   - recumbent length,
   - head circumference,
   - skinfold thickness,
   - bioelectrical impedance,
   - stable isotope, dual energy x-ray absorptiometry, or
   - other physical body measurements or body composition measurements

2. Which anthropometric and /or body composition measures are **necessary** for adequate clinical evaluation of normal physical growth of infants between birth and 6 months of age consuming new infant formula?

3. The metrics above can be evaluated as static (attained growth) or variable (rate of change). Please comment on the values and merits of each method. What determines the appropriate "unit" for analyses e.g. individual growth performance, group comparisons, etc.

4. At the present time, do any of these measures of physical growth have accepted scientific agreement concerning predictive value for physical and pathophysiological outcomes in later infancy, childhood, adolescence or adulthood? Relevant outcomes that may involve nutritional adequacy in early infancy may encompass (for purposes of this meeting discussion) nutrition-related conditions that may evolve to, for example, obesity, diabetes mellitus, or hypertension.

COMPARATORS FOR THE EVALUATION OF NORMAL PHYSICAL GROWTH

5. What are the values and merits individually, and in combination, of each of the following types of comparisons in infants fed a test formula versus control formula(s) for assessing normal physical growth?

- concurrent controls (demonstration of bioequivalence)
- reference data (comparison with normative data for populations and subpopulations)
- historical controls
- other

6. For the adequate clinical evaluation of normal physical growth, which of the above comparisons is/are necessary?

7. For the purpose of evaluating normal physical growth of infants fed new formulas, what criteria should appropriate infant growth references meet (e.g., feeding history, gestational age at birth, sex, racial background, socio-economic status, other) in comparison to the study population? In comparison to the population intended to consume the formula? Under what circumstances should such a reference serve as a standard?

CONTROL FEEDING COMPARATORS

8. What are the values and merits of comparisons of each of the following types of control feedings for assessing normal physical growth when considering infants fed new infant formulas? Please consider these comparisons in light of parallel merits of concurrent bioequivalence data versus comparison with reference (normative) data.

- (current infant formula (IF) + new ingredient) vs. (current IF) vs. (breast milk)
- (current IF + new ingredient) vs. (current IF)
- (current IF + new ingredient) vs. (breast milk)
- (current IF + new ingredient) vs. (formulas fed to historical infant cohort(s) (e.g., Iowa data))
- (current IF + new ingredient) vs. (references that may include various types of feedings in such reference populations (e.g., NCHS and WHO))
- (IF + new ingredient)* vs. (any of the above controls)

*test formula contains new ingredient but the test formulation differs from the new formula that firms intends to market containing the new ingredient

9. For adequate clinical evaluation of normal physical growth, which of the above comparisons are necessary?

CHANGES IN INFANT FORMULA COMPOSITION

10. With regard to formula composition changes, please describe general principles and criteria that can be used to determine the need for a clinical study intended to provide assurance of normal physical growth.

Table 1

Infant Formula Ingredients	Examples of changes to ingredient	Examples concerning the need for a clinical growth study to assure no adverse effects on normal physical growth
Protein	**Source**: Soy vs. cow milk vs. goat milk. **Processing**: Stripping (e.g., removal of lactose, isoflavones, minerals), hydrolysis (partially to extensively hydrolyzed).	• A change from one protein source to another. • Processing of soy protein to remove isoflavones. • A change from a non-hydrolyzed protein to hydrolyzed (e.g., partially to extensively) protein
Fat	**Source:** New fats and oils, and oil blends, various long chain polyunsaturated fatty acids containing oils (LCPUFAs). **Processing:** Structured fats (e.g., rearranged or fractionated fats).	• Addition or substitution of one or more new fat sources • Addition or substitution of new structured fats
Carbohydrate	**Source:** New, previously unused carbohydrates, novel sugars (e.g., tagatose), oligosaccharides (simple or complex). **Processing**: Lactose removed from ingredients derived from milk	• Addition of novel sugars or other new carbohydrate. • Processing of whey to remove lactose.
Minerals/ Vitamins	**Source**: Various mineral salts and various forms of vitamins. **Concentration**: Increased minerals and vitamins. **Processing**: Removal of minerals from infant formula ingredients. Reduction of heat-labile vitamins during thermal processing	• Changes to the source (e.g., chemical form or precursor form) and concentration of minerals and vitamins • Changes to the bioactivity/bioavailability of minerals and vitamins during processing • Processing of ingredients derived from milk to remove minerals (e.g., reduced minerals whey)
Other	**Technical effect ingredients**: Emulsifiers, thickeners, food colors, flavors, antioxidants. **Purported physiological effect new ingredients**: Probiotics, prebiotics, oligosaccharides, amino acids (e.g., glutamine, arginine), glycolipids, glycoproteins (e.g., lactoferrin), immunoglobulins.	• New addition or increased level of a technical function ingredient. • Addition of new ingredient(s) (singularly or in combination) with purported physiological effects.
New uses of previously used or studied ingredients	**Combinations of macro ingredients previously used** in other infant formula. **Technical effect ingredients previously used** in other infant formula **Purported physiological effect ingredients previously used** in other infant formula	• New combinations of macro ingredients that have been used separately in various currently marketed US infant formulas (made by the same manufacturer or made by other manufacturers) but not together in the same formula matrix. • Addition of new ingredient(s) (singularly or in combination) with purported physiological effects that have been used or studied in other currently marketed US infant formulas (made by the same manufacturer or made by other manufacturers) but not in the particular formula matrix.