BACKGROUND AND QUESTIONS

FOOD AND DRUG ADMINISTRATION FOOD ADVISORY COMMITTEE
INFANT FORMULA TASK FORCE

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 Infant Formula Task Force is being asked at this meeting to consider two issues.

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 Task Force 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.)

The Task Force is also being asked to consider the types of changes in infant formulas that should be accompanied by a clinical study in order to provide assurances of normal physical growth. Considerations could include, but are not limited to, 1) interactions affecting potential bioactivity or bioavailability among individual formula components in an infant formula matrix during formulation, processing, and storage and 2) 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.

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. Considering the values and merits individually, and in combination, please group the following metrics in terms of their clinical usefulness as endpoints for assessing normal physical growth.

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

2. Which of the above 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?

3a. The metrics above can be evaluated as attained (absolute growth) or velocity (rate of change) of measures. Please comment on the distinguishing values and merits of each static or variable method in the assessment of normal physical growth

3b. The outcomes above can also be evaluated as individual infant data or as group comparative data. Please comment on the values and merits of using individual or aggregate data in the assessment of normal physical growth.

COMPARATORS FOR THE EVALUATION OF NORMAL PHYSICAL GROWTH

4. For adequate evaluation of normal physical growth, below are examples of clinically distinct reference groups.

- ?? concurrent controls (concurrent data or population cohorts for demonstration of bioequivalence)
- ?? reference data used as controls (comparison with previously collected normative data for populations and subpopulations)
- ?? historical controls
- ?? other

a. What are the distinguishing values and merits of each type of reference group for the assessment of normal physical growth?

b. Please rank these reference groups based upon the ability of the respective control population to contribute to an assessment of normal physical growth in the population intended to consume the formula.

c. What is the role of such a reference group?

5. For the purpose of evaluating normal physical growth of infants fed new formulas, what criteria should appropriate infant growth reference groups meet (e.g., each or selectively, 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?

CONTROL FEEDING COMPARATORS

6. Listed below are examples of control feedings (clinical comparators):

- ?? (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)

a. What are the most distinguishing values and merits of each of these types of comparisons in infants fed a test formula vs. a comparative feeding for assessing normal physical growth?

b. Please rank these comparisons based upon their potential for generating clinical data which would be most relevant to an assessment of normal physical growth.

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

CHANGES IN INFANT FORMULA COMPOSITION

7. With regard to formula composition changes:

a. 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.

b. Describe some of the specific changes in infant formula that would reasonably be expected to be accompanied by a clinical study to demonstrate 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, 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.