

QUALITY FACTORS FOR INFANT FORMULA

ORAL TESTIMONY

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INTRODUCTION

On behalf of the U.S. infant formula industry,* we appreciate the opportunity to address members of the FDA's Food Advisory Committee (FAC) and the Expert Panel on Infant Formula (Expert Panel) regarding quality factors for infant formulas.

US infant formula manufacturers are acutely aware of the importance of our products to infant nutrition and health. We recognize that infant formulas are often the sole source of nutrition for infants, and that design, manufacture, and control of infant formula, therefore, require special care. Additionally, the industry fully acknowledges that breastfeeding is the preferred feeding method for most babies, and manufacturers constantly work on improving their formulas to incorporate as much as possible the nutritional benefits provided by human milk. Formulas on the market today are designed to meet or exceed nutritional standards recommended by the Committee on

* Mead Johnson & Company; Nestle USA, Inc., Nutrition Division; Ross Products Division, Abbott Laboratories; Solus Products LLC; and Wyeth Nutrition.

Nutrition of the American Academy of Pediatrics and mandated by the Infant Formula Act of 1980 (IFA) as amended in 1986. It is our responsibility, as manufacturers, to have the best application of science and assure any new or changed formulation will support normal growth and meet required quality factors.

Next I would like to identify what we believe are the critical issues for consideration before going on to discuss them in greater detail.

- First, the process by which the important issue of quality factors is addressed should be a thorough one, allowing sufficient time for the best input, so that the outcome is in the best interests of infants' health.
- Second, clinical studies in infants should be scientifically, medically and ethically justified.
- Third, when studies are needed, and what they encompass, should take into consideration the practical scientific knowledge best obtainable from the manufacturer. And, as appropriate, this knowledge may also include relevant international experience.
- Fourth, any generalization of findings from a clinical study in one population to other populations, in the absence of specific clinical

data, should be reviewed on a case-by-case basis for its scientific merit and relevance.

- Fifth, the infant formula industry operates under a comprehensive pre-market notification process, unlike other foods in the US.

Based on the best interests of infants and sound science, the law requires pre-market notification and not pre-approval of new infant formulas.

Now I will discuss each of these five important points in greater detail.

KEY POINTS

Thorough and Considered Process

First, we strongly recommend that any deliberations or determinations on quality factors for infant formulas take the time necessary and offer the opportunity for the best scientific, medical and practical input available--keeping in mind that the industry already has access to the best scientific, medical and practical input both internally and from academic consultants, and is already held fully responsible under the law for ensuring the quality of its formulas.

The infant formula industry looks forward to providing additional comments and having the opportunity to actively participate in any deliberations affecting infant formula requirements since we are most intimately and most broadly equipped to address these issues. For example, we have provided extensive comments to the Life Sciences Research Office (LSRO) of the American Society for Nutritional Sciences regarding their review of nutrient requirements for both term and preterm infants, as well as to the American Academy of Pediatrics on clinical testing of new infant formulas .

Scientific, Medical and Ethical Considerations

Second, we are concerned about an apparent recent trend for FDA to require growth studies unsupported by scientific need. Such a practice does not consider all of the relevant data and ignores FDA's own ethical guidelines issued as an interim rule in 2001 to provide additional safeguards for children enrolled in clinical studies involving FDA-regulated products.¹ It is critical to distinguish between what is truly needed and can be provided by a growth or other clinical study, and what may be primarily of academic interest. It would be especially troubling if studies that were unnecessary, invasive or

● unreliable were deemed necessary because of an inappropriate assessment of what is "required."

It is critical that FDA's ethical guidelines (as to when it is appropriate to perform testing in infants) be integrated into FDA decision-making so as not to subject infants to unwarranted testing. It also is important to recognize the practical difficulties involved in doing unnecessary research in infants (e.g., cost of study, delay in time to market, and scarcity of subjects).

● For guidance on this issue, including whether growth or other studies are needed, we recommend FDA be encouraged to rely more heavily upon those with pediatric nutrition expertise who regularly conduct infant clinical studies, instead of relying on theoretical arguments for growth studies that are not based on sound, practical scientific experience.

What Studies Are Needed?

● Third, while it is very important that FDA provide general guidance on when and what clinical studies may be needed, any regulations on

the actual conduct of growth or other studies should provide a framework and should not be overly prescriptive. FDA earlier proposed the following two quality factors, namely that infant formulas shall (1) support normal growth, and (2) contain protein of sufficient quality to meet the protein requirements of infants.² Manufacturers thus currently establish that any new infant formula (including an existing formula to which a major change has been made) meets these required quality factors. It is important that any further clarification of quality factors for infant formula be science-based and, if it is deemed necessary to have additional guidelines, they should be transparent with appropriate exemptions established. Any required tests should be biologically informative and reasonably well-standardized.

Decisions on when growth studies are required should be based on the manufacturer's knowledge and experience in specific ingredient additions, product manufacture, the level and reason for addition of the ingredient, and the anticipated outcome that could be expected from the conduct of such a trial. When a clinical study is warranted, numerous criteria should be considered to make informed decisions on which type of study (growth trial or other) is most appropriate.

These decisions should consider the type of change ("major" or "minor"); the clinical study's scientific merit; strong ethical considerations, such as the invasive nature of the study; and overall medical justification. This also includes practical scientific knowledge best obtainable from the manufacturer.

Generalization of Clinical Study Findings

Fourth, any generalization of findings from a clinical study in one population to other populations, in the absence of specific clinical data, should be reviewed on a case-by-case basis for its scientific merit and relevance. The FAC has been asked "to discuss the scientific issues related to the generalization of findings from a clinical study using preterm infant formula consumed by preterm infants to a term infant formula intended for use by term infants." It is important to recognize there is no definitive answer for this issue. For example, there may be instances when data are not relevant. There also are cases when data may be informative, but not definitive. However, there also may be circumstances when data from a study are applicable and therefore can be appropriately extrapolated to another formula or infant population. Any extrapolation of data must be

justified by generally accepted scientific principles and be reviewed for scientific merit while meeting the applicable legal standards (e.g., classes of compounds, sources of ingredients, intended use, and bioavailability). Additionally, each situation must be examined on a case-by-case basis and an informed decision made on the basis of the relevant science.

For example, with respect to bioavailability, a nitrogen balance study in preterm infants showing absorption of a protein source would be expected to be applicable to term infants. However, the mechanism of absorption for some nutrients differs with age (e.g., calcium-mass balance vs. vitamin D dependency). In addition, there is recent evidence that trace elements may be more absorbed by premature infants. In these situations, the results from a preterm study would not be applicable to a term infant formula.

This leads to our fifth point.

Infant Formula Industry Operates Under a Comprehensive Pre-Market Notification Process

It is important to recognize that the infant formula industry has been operating by law under a notification process for over 20 years with a remarkable record of providing safe and useful infant formulas.

Manufacturers must notify FDA 90 days prior to marketing a new infant formula or an existing formula which has had a major change.

Under this process, infants have been well-protected, and the industry and FDA should take great pride in the safety of infant formula. FDA's infant formula review responsibility is *not* a pre-approval process. The Infant Formula Act of 1980 "did not authorize any form of preclearance by the FDA for the marketing of an infant formula." ³

In 1986, Senator Metzenbaum's initial amendment to the Act 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." ⁴ This congressional intent remains in place today.

In summary, it is the manufacturer's responsibility to assure any new or changed formulation will support normal growth and meet the required quality factors. Thus, we believe it is important for the infant formula industry, FDA, FAC and the Expert Panel to work together to develop and maintain high scientific standards relating to infant formula. We further recommend that Congress appropriate the necessary resources to support the expertise needed by the Agency to facilitate its important regulatory responsibilities for infant formulas.

REFERENCES:

1. Interim Rule - Additional Safeguards for Children in Clinical Investigations of FDA-Regulated Products [66 *FR* 20598], Tuesday, April 24, 2001
2. Current Good Manufacturing Practice, Quality Control Procedures, Quality Factors, Notification Requirements, and Record and Reports, for the Production of Infant Formula, Sec 106.96(a), [61 *FR* 36153], Tuesday, July 9, 1996.
3. Report by the Committee on Labor and Human Resources United States Senate, Infant Formula Act of 1980, August 26, 1980. Pages 5 - 6.
4. Congressional Record - Senate, September 27, 1986. Pages S14046-7.