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**Wyeth**

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General comments on behalf of Wyeth Nutrition  
FDA Food Advisory Committee of April 4 & 5, 2002

Dear Committee Member:

The Food Advisory Committee has been asked to consider the following issue:

*"The committee will also be 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."*

(Federal Register 3/19/02; 67(53):12572)

This is an important issue. As an infant formula company we take as our primary responsibility the safety of the infant. All our clinical programs highlight the fact that the determination of the suitability of a term infant formula is a complex matter. Our ability to generalize data from preterm studies to term infants is guided by the following principles:

- A clinical study in preterm infants is not sufficient *by itself* to make generalizations about term infants.
- All data related to a new infant formula should be fully considered regardless of whether the study was conducted in term or preterm infants.
- Data from well-controlled studies of preterm infants may be generalized to term infants as part of a larger body of safety and efficacy data.

What follows are highlights concerning the utility of preterm data in the evaluation of term infant formula. We will show that in some instances, the data is readily generalizable while in other instances, the data is especially relevant. Also, we will discuss how supporting data can assist in generalizing findings from studies in preterm infants to a term infant population. Lastly, we will provide comments on the infant formula matrix, specifically the similarities and differences between preterm and term infant formulas.

These highlights will be further detailed in a presentation to the Food Advisory Committee by Eric L. Lien, PhD., Vice-President, Nutritional Research & Development, Wyeth Nutrition.



### **Cases where preterm data can be readily generalized to full-term infants**

Preterm infants and term infants are on a continuum of physiologic maturity and nutritional needs. Most certainly there are differences in physiologic maturity between preterm infants born at 34 weeks post conceptional age (PCA) and those born at 25 weeks PCA. Late preterm infants closely approximate the physiologic maturity of term infants. Thus, a study in preterm infants born at 34 weeks of gestation age and continued well past 40 weeks PCA could be more easily generalized to full-term infants than a study in preterm infants born at 25 weeks of gestational age and of relatively short duration. Examples of the close relationship between preterm infants born relatively close to 40 weeks and infants born at term can be seen in studies of fat and protein digestion.

In the case of dietary fat, preterm infants born at 31-32 weeks PCA digest and absorb 91.2% of dietary fat during the first week of life; term infants similarly, digest and absorb 91.7% of dietary fat in the first week of life. Both preterm and term infants increase efficiency of dietary fat absorption to 97% at similar rates over the first five months of life (Rings et al. *Pediatr. Res.* 51: 57-63, 2002). Thus, studies on the efficiency of absorption of a new fat blend in preterm infants at 32 weeks PCA would likely be generalizable to efficiency of absorption of the fat blend in term infants.

For dietary protein, nitrogen absorption and retention is relatively efficient even in preterm infants (Kashyap et al. *Am. J. Clin. Nutr.* 52: 254-262, 1990). Protein requirements are much higher for preterm infants than for term infants to allow for nitrogen accretion similar to intrauterine growth rates. A Life Science Research Office (LSRO) report, commissioned by the FDA, on the nutritional needs of preterm infants noted that premature infants (after more than 32 weeks of gestation) are considered equal to full-term infants in their ability to digest protein (LSRO, *Nutrient Requirements for Preterm Infant Formulas*, 2001; p. 365). Thus, evaluation of the digestion and absorption of a new protein source in preterm infants would provide important information about the protein source's digestion and absorption in term infants.

### **Cases where preterm infant studies can be especially relevant to term infants**

Preterm infants are more likely to exhibit adverse events in clinical trials than term infants. Therefore, the adverse experience profile observed in preterm studies helps to provide assurance that a similar or more favorable profile would be observed in a term population. Also, preterm infants have less tissue and metabolic reserve, and are more vulnerable to environmental factors than term infants. If there are data that

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show no increase in adverse events when a substance is studied in preterm infants, it is reasonable to generalize that, at a comparable exposure in term infants, there should not be a higher risk of adverse events.

In addition, since nutrient requirements are higher in preterm compared to term infants, this population may be particularly sensitive to growth perturbations. This parallels the FDA proposal to require that growth outcomes for a term formula be assessed during the first postnatal months when growth is most rapid and nutrient needs are greatest rather than later in the first year of life. Due to the rapid growth rate of preterm infants, growth assessment of a new substance added to preterm formula can be very useful in assessing addition to term formula. Therefore, data from a preterm infant growth study comparing a preterm formula containing the substance under evaluation to a control formula will be a sensitive indicator of the overall safety of the new substance and the safety of this substance when interacting with an infant formula matrix (see, for example, the assessment of long chain polyunsaturated fatty acids (LCPs) on growth in a preterm population: Vanderhoof et al. *JPGN* 29: 318-326, 1999).

## **Generalizing data from preterm to term infants requires supporting data**

The more that is known about a substance under evaluation, the greater the confidence in any generalization of preterm data to term infants.

Examples of strong supportive data include:

- The substance is a normal, nutritional constituent of human milk.
- Studies have characterized the safety, metabolism and tissue accretion of the substance in both preterm and term infants.
- Studies have optimized the concentration of the substance in formula to produce comparable outcomes in breastfed and formula-fed infants.
- The substance has a successful history of use in term or preterm infant formula.

Studies on GRAS (Generally Recognized As Safe) substances can also support generalizations from preterm to term infants. A GRAS safety assessment considers important conditions of use such as form, bioavailability, dose and adverse events. When a substance has been designated GRAS based on both preterm and term infant studies (e.g. GRAS notice 041 on ARASCO and DHASCO from Martek Biosciences), then one can have greater confidence in the safety across both groups of infants.

In addition, generalizations may be made with greater confidence when there is enough data to allow conclusions to be drawn in comprehensive reviews, e.g. in a meta-analysis or in a systematic Cochrane review. One feels comfortable to generalize from a study in preterm infants if there are separate comprehensive reviews about the



tested substance in preterm infants and in term infants that reach the same conclusion. For example, the studies reporting effects of adding LCP's to preterm formula and to term formula have been separately reviewed in meta-analyses and in Cochrane reviews and in all cases the conclusion has been reached that there are no deleterious effects of the LCP's on growth.

### **The infant formula matrix differs between preterm and term infant formulas**

Differences in the formula matrix must be considered when generalizing findings from preterm to term infants. However, term and preterm formulas are constrained with regard to protein, fat, calories and micronutrients concentrations. If the metabolism of the substance is known and the independent interactions of the substance with matrix components is also known, then the effects of the limited range of formula matrices can be anticipated and evaluated. In these cases, the experience of a manufacturer with both preterm and term formulas adds confidence to generalizations across different matrices because manufacturers routinely collect data about the stability of nutrients in the formula and ensure that nutrient concentrations meet requirements throughout shelf life. Generalizations are enhanced when data are available about the bioavailability of the substance in the matrices under consideration. In addition, if the substance has produced similar growth, safety and efficacy outcomes in a variety of formula matrices (e.g. studies by different manufacturers), then the effects of the preterm versus term formula matrix may be minimal.

### **Conclusions**

A study of preterm formula in preterm infants is not definitive by itself to make generalizations to term formula for term infants. But, studies of preterm formula in preterm infants can provide valuable information in the assessment of comparable term formulas for term infants. Our ability to generalize from preterm to term infants depends on several factors including the quality of the preterm infant study, the relative maturity of the preterm infant group, the amount of available published (and unpublished) supportive data, and the extent of interaction between the substance being tested and the infant formula matrix. Data from preterm infant studies, if available, should always be considered as part of any supporting data package for a new term infant formula.

Respectfully submitted,

Wyeth Nutrition