

# American Academy of Pediatrics

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Dockets Management Branch (HFA-305)  
Food and Drug Administration  
5630 Fishers Lane, Rm 1061  
Rockville, MD 20852

Re: Docket No. 1995N-0309

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To whom it may concern:

On behalf of the 57,000 members of the American Academy of Pediatrics (AAP), I offer the following comments regarding the Proposed Rule, *Current Good Manufacturing Practice in Manufacturing, Quality Control Procedures, Quality Factors, Notification Requirements, and Records and Reports for the Production of Infant Formula*, originally published in the *Federal Register* on July 9, 1996 (61 FR 61534) and re-opened for public comment on April 28, 2003 (68 FR 22341).

The AAP is the national professional organization representing physicians who provide health care to our infants, children, and adolescents. In that role, the AAP has developed extensive policy guidelines regarding adequate and safe diets for these age groups.

## Issue #1 Safety of powdered formula

Given the recently reported cases of *E. sakazakii* infection in newborn infants receiving powdered formula, microbiologic standards for powdered formula should be established. While sampling large batches of product can be problematic, and product sterility cannot be absolutely assured, all powdered formula should be *E. sakazakii* free.

The AAP also recommends that the standards regarding powdered formula be the same for premature as well as term infants. The AAP sees no reason that they should be different, as the absolute risk, even to term infants, is not zero. Powdered formula products should not be consumed by premature infants before 44 weeks gestational age, or by any immunocompromised child. With few exceptions (amino acid and metabolic formulas), "commercially" sterile liquid products are available for these populations. The total elimination of powdered human milk fortifier will not be possible for the premature infant. While there is a

95N-0309

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liquid preparation, many of these infants are unable to tolerate the added volume the liquid fortifier requires.

#### **Issue #2 - Addition of Bifidobacterium and Streptococcus to infant formula**

The AAP has concerns regarding the generally recognized as safe (GRAS) status of Bifidobacterium and Streptococcus for infant formula intended for infants over 4 months of age and therefore recommends against its addition. The risks and benefits of such formula have not been determined. The biology of the microflora of the infant intestine is only partially understood; there is variation of the flora along the length and within the layers of the intestine, and the flora change with age as the infant grows and matures. It is unclear how manipulation of the microflora might alter these developmental processes. While probiotics, such as Bifidobacterium and Streptococcus, appear to have some beneficial effects in terms of decreasing permeability and enhancing local and system immune response, the mechanisms of these effects are not known nor is the possibility of long-term adverse effects entirely excluded (Ghisolfi J, et. al. Infant formula supplemented with probiotics or prebiotics: never, now or someday? *J Pediatr Gastroenterol Nutr.* 2002; 467-469).

Further the AAP is concerned about monitoring these microorganisms in powdered formula products and distinguishing them from contaminating organisms. Identifying the degree of sterility of such products might become problematic. The AAP also recognizes the risk that infants not in the intended use group would receive this formula, as there is presently no formula on the market that is only intended for infants over 4 months of age.

#### **Issue #6a - Clinical growth studies for new or reformulated infant formulas**

The AAP recommends that a clinical growth study be required for any new infant formula, change in the infant formula, or change in the packaging of infant formula. The AAP further recommends that the manufacturer be made responsible for demonstrating that a formula-growth study is not needed rather than exempting it from conducting studies in a finite number of circumstances. Infant formula is unique in that it can be the sole source of nutrition for an infant for an extended period of time and during a most vulnerable time. Growth alone as the sole outcome measure may not be adequate. As the changes in formulas become more subtle, such as with the recent addition of long chain polyunsaturated fatty acids (LC-PUFA), outcome measures must also include other relevant effects such as those on visual acuity and intelligence. These effects may only become measurable months to years after the infant is no longer taking formula.

**Issue #6b - Growth standards for formula studies**

Growth may or may not be the crucial outcome measure in future formula studies. Further, "optimal" growth and development have yet to be defined. As such, the AAP feels strongly that a concurrent control group is the optimal comparator and recommends a concurrent breastfeeding control group be used.

**Issue #6c - Age of enrollment and duration of participation**

The crucial period for formula studies in the past has been during the time of exclusive formula feeding, a time when the formula is supplying all of the infants' needs. Once complementary foods are introduced, the effects of the formula, negative or positive, will become blurred. Thus the earlier the infant is enrolled in the study the longer the observation time.

In the past, the length of observation has been 4 months. The AAP currently recommends the introduction of complementary foods between 4 and 6 months. In order to ensure a minimum 4-month observation time without interference from complementary feedings, enrollment must occur by 14 days of age.

As discussed above, the AAP anticipates that future formula studies will need to extend for years rather than months to detect the subtle effects of formula feedings. This change will require manufacturers to conduct post-marketing surveillance as a part of every formula study.

The Academy welcomes the opportunity to comment on this important matter. Please contact me or Molly Hicks in the Academy's Washington Office (202/347-8600) if we can be of any further assistance.



Sincerely,  
Carol D Berkowitz, MD, FAAP  
Vice President  
American Academy of Pediatrics

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