Principles and Criteria for Determining when a Clinical Study is Needed to Assure that Normal Physical Growth of Infants will not be Adversely Affected
Clinical Perspective

A White Paper

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by

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General Principles and Criteria for Determining When A Clinical Study is Needed to Assure that Normal Physical Growth of Infants Will Not Be Adversely Affected

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Introduction

There is global, unanimous agreement that human milk is the preferred food for human infants born at term and that breast feeding is the preferred method of its delivery. Nonetheless, for various legitimate reasons, infant formulas are the sole source of nutrient intake for many term infants during the first four to six months of life and a significant source of nutrients during the remainder of the first year of life. Further, because of the special needs of infants born prematurely (1), the American Academy of Pediatrics has acknowledged that growing preterm infants might benefit from the enriched nutrient levels present in formulas designed specifically for their increased nutrient requirements (2). Although infant formula is a food, its contents and safety must be more stringently regulated than ordinary foods because it is the sole source of nutrition for a critical, vulnerable period of human development and because the infant cannot voluntarily chose his or her food or mode of feeding during this period.

Currently available infant formulas are a triumph of industrial food sciences. At the beginning of the last century, an infant who could not be breast-fed was likely to die. In developed countries at the end of the century, the mortality, health, growth and development of formula fed infants are largely indistinguishable from those of infants who are breast-fed. Similarly, the American Academy of Pediatrics Task Force on *Clinical Testing of Infant Formulas with Respect to Nutritional Suitability for Term Infants* acknowledged that "the safety record of the infant formula industry, although not unblemished, has been remarkably good" (3).

Neither term infants nor preterm infants fed formulas now commercially available in the United States show any known nutrient deficiencies that are the direct result of feeding the formula *per se*. This observation provides support for the position that infant formulas as currently constituted contain all the known essential nutrients in sufficient amounts. For this reason, requests for addition of new nutritive and non-nutritive substances to infant formulas are likely to be based on proposed benefits other than nutrient adequacy.

The following guidelines and criteria reflect my views on when a human infant growth study is necessary. They do not take into consideration the constraints of current statutes or regulations. Neither do they consider the associated costs, the ethical issues of research involving human infants or the proper design of such studies.

Guidelines

Guideline #1: Measurement of growth is an integral and necessary component of every clinical nutrition study involving human infants.

When an immature animal has an intake of dietary nutrients that exceeds the quantities required to satisfy the basic needs of metabolic processes and that provides sufficient energy to drive these, growth occurs. The measurement of growth, then, is a valuable indicator of adequacy. Further, growth measurements have two important advantages in clinical studies. First, growth can be measured highly accurately, precisely, and non-invasively. Secondly, growth is a non-specific index of adequacy and, therefore, likely to be a more sensitive marker of unanticipated detrimental effects. In 1988, an American Academy of Pediatrics Task Force concluded that "determination of rate of gain in weight is the single most valuable component of the clinical evaluation of infant formula" (3). A general guideline, I concur with this opinion and, in this context, measurement of growth (i.e. " a growth study") is an integral and necessary component of every clinical nutrition study involving human infants.

Guideline #2: Infant growth studies require both the measurement of weight and of length.

The AAP Task Force also considered "it unlikely that a significant difference in length gain between an experimental and control group will be demonstrated in the absence of a significant difference in weight gain (3)" and thus concluded that length gain was not an essential part of clinical testing of infant formulas. While the latter position is both reasonable and intuitive, I am not sure that there are systematic data from published infant formula studies to support the position.

Because the hormonal, growth factor, and gene regulatory controls of linear growth are different from those correspondingly controlling weight gain, and because measurement of linear growth is accurate, precise, simple and non-invasive, I believe that an essential guideline for clinical studies of infant formulas requires both the measurement of weight and length. Thus, when I use "growth" in the remainder of this position paper, I refer to both linear and ponderal growth. However, because there are no clear and enduring long-term relationships among body composition characteristics measured in infants of the ages pertinent to infant formula studies, and because there are no firmly established, prospective relationships among these infantile characteristics and adult health or disease, I do not include body composition measurements in my definition of growth studies.

Guideline #3: Animal studies are never a sufficient substitute for human growth studies.

Pre-clinical animal studies are often necessary, particularly for totally new compounds that have not previously been added to infant formulas. Nonetheless, known species specific aspects of various milk components and species differences in numerous growth and developmental characteristics seriously limit confident extrapolation of data from any animal model to conclusions about human growth. Therefore, in my opinion, an

additional practice guideline is that animal studies are never, in my opinion, a sufficient substitute for human growth studies.

Guideline #4: The presence of a substance in human milk, *per* se, is not sufficient justification for eliminating the need for a growth study.

The rationale for adding substances to formulas is frequently based on the presence of the material in human milk. There is clearly some justification for this rationale in the case of essential nutrients although, even here, the human milk content of selected essential nutrients is not necessarily optimal, particularly for the growth of high risk infants born very prematurely. However, the rationale is on much weaker grounds when applied to non-essential nutrients or to non-nutritive compounds present in human milk. Some components of human milk are actively secreted into the milk, presumably for a purpose. Others, however, appear in human milk *pari passu* with the movement of water. Further, millions of infants in the United States have been fed with formulas devoid of the majority of the known non-nutritive substances present in human milk without apparent detrimental effects. Thus, recently, the Committee on Nutrition of the European Society of Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN), in a position paper on *The Nutritional and Safety Assessment of Breast Milk Substitutes and Other Dietary Products for Infants* stated that "gross compositional similarity [i.e. to human milk] is not, in itself, an ideal determinant or indicator of the safety and nutritional adequacy of dietary products for infants. A better approach is considered to be the comparison of outcomes in infants fed such products with those seen in healthy infants who have been breast-fed exclusively for 4 to 6 months" (4). I concur with this expert panel opinion and, as a general guideline, I would not excuse necessary growth studies on the basis of a substance's presence in human milk alone. However, since many additions or changes to formula are modifications of currently-marketed products, the appropriate control growth might more suitably be infants consuming the corresponding currently-marketed formula rather than "infants who have been breast-fed exclusively".

Guideline #5: Data from post-marketing experiences in other countries, *per se*, is not a sufficient substitute for a pre-market clinical growth study.

Most postmarkeing surveillance is of an uncontrolled "non-experimental" nature. The validity of postmarketing data depends on health professionals reporting adverse events. There is substantial evidence that significant underreporting of serious events occurs for various reasons, including lack or recognition of the event's relationship to the responsible agent, attribution of the event to another cause, personal reluctance to admit potential errors in clinical judgement, potential liability issues, and the practical nuisances associated with proper reporting. Further, given the range of variation of normal infant growth due to genetics and given the additional confounding influences of illness and caregiver practices on growth, it is likely that health professionals would attribute at least some alterations in growth to causes other than the infant's formula *per se*. These considerations make postmarketing studies relatively insensitive to or unlikely to identify small but significant differences in growth that would be uncovered by

properly controlled pre-market studies. Therefore, as a general guideline, post-marketing studies cannot substitute for properly controlled clinical growth studies.

Criteria

Criterion #1: An infant growth study is required for all substances added to formula under the rationale of influencing growth.

It would appear axiomatic that any substance(s) added to formula to influence growth should be tested in a human infant growth study. This criterion is phrased for the particular case at hand, namely requirements for growth studies, but it is merely a specific case for a more general principle, that is substances added to infant formula for "Effect X" should be tested in human studies with "Effect X" as a primary end-point variable. This position was stated in a somewhat different fashion by the Working Group on the Nutritional Assessment of Infant Formulas of the Committee on Medical Aspects of Food and Nutrition Policy in the United Kingdom (5). This expert body concluded that "An hypothesis to justify the innovation should be stated from the outset, including the characteristics of the infants for whom the new formula is intended. For most innovations the goal should be an hypothesised functional or clinical benefit based on defined outcome measures" (5). They further stated that "any modification whether or not within the statutory regulations, which is hypothesized or claimed to have significant advantages, or which incorporates novel foods or is derived from novel food processes, should be subject to clinical trial" (5). These recommendations seem to lead logically to the conclusion that essentially all new additions to infant formulas would require a clinical study and, since assessment of growth is an essential fundamental element in infant clinical studies, would thus, *de facto*, require a growth study. Indeed, the first general principle recommended by the advisory body was "All modifications to infant formulas should be assessed nutritionally" (5). Since I am unaware of how a human nutritional effect can be convincingly assessed or established without a human study, I conclude that this was the intent of the Working Group, an opinion affirmed by communication with a panel member (Prof. Peter Aggett, personal communication).

Criterion #2: An infant growth study is required for added compounds known to affect hormones, growth factors, or metabolites that regulate or control growth.

Ian equally axiomatic criterion is that substances known to affect the secretion, disposition or action of growth promoting hormones, growth factors, and other metabolic regulatory substrates should not be added to infant formulas without appropriate human growth studies. Similar considerations hold for substances known to modify the expression of genes that contribute to growth or to energy and macronutrient fuel metabolism. The number of compounds that satisfy these conditions are sizable and continue to increase on a regular basis as more scientific information becomes available.

Criterion #3: An infant growth study is required for all formula additions, reductions or changes that result in levels of essential nutrients outside of established ranges.

Under provisions of the federal Food, Drug, and Cosmetic Act, current regulations (21 CFR 107.100) require term infant formulas to contain no less than specific levels of 29 nutrients and no more than specified levels of 10 of these nutrients (6). "Formulas intended for preterm infant feeding are regulated as exempt infant formulas under the Infant Formula Act of 1980 and its 1986 amendment. ... Exempt infant formulas may have nutrients or nutrient levels that are different from those specified in 21 CFR 107.100" (1). The specifications in 21 CFR 107.100 are now more than a decade old and would appear inadequate given (a) the nature of substances considered potentially appropriate for addition to infant formulas, (b) far more current expert committee recommendations on the Dietary Reference Intakes for infants (7) and recent expert panel recommendations of nutrient requirements for term (8) and preterm infant formulas (1). FDA requirements for the nutrient content of infant formulas should be brought up to date and reflect expert consensus specifications based on current advisory panel data (1,7,8). Ranges thus established would form the basis for a criterion that requires a clinical growth study for all formulas that do not fall within range limits.

Once new nutrient concentration ranges are codified in federal regulation, any formula whose nutrient content fell out-of-range would be an illegal formula that could not be marketed. However, at some point, new compelling nutrient requirement data or other advances in nutritional science might indicate a need to reassess established ranges. In this context, nutrient additions, reductions or changes that fall outside the specification limits would require validation with a clinical study of efficacy and safety that included growth as one end point.

This position agrees with a similar position espoused by participants in a recent workshop sponsored by ESPGHAN and the Child Health Foundation of Munich (9). The approximately 50 participants from "academia, infant food industry, consumer organizations, the Health and Consumer Directorate General of the European Commission and the food regulatory bodies of some European Union member states" agreed that a growth study "was needed when there were changes in energy density beyond established limits, significant changes in macronutrient composition, new or markedly modified nitrogen sources, concerns about bioavailability or macronutrients, or any other concern that growth could be altered." (9)

It is important to also note that the U.K. Committee on Medical Aspects of Food and Nutrition Policy also concluded that "...it cannot be assumed that formulas which fall *within* [italics mine] the compositional requirements of [EU] regulations will necessarily perform satisfactorily." (5) because of a wide variety of know nutritional effects such as positive or negative interactions among nutrients and the effects of one nutrient on the absorption or metabolism of another.

Taken together then, these combined recommendations agree with and further expand the circumstances that warrant clinical testing as defined by the American Academy of Pediatrics Task Force in 1988 (3).

Criterion #4: Addition of an entirely new compound to infant formulas requires a clinical growth study.

New compounds are those which have not hitherto been present in infant formulas and fall into two major classes: (a) substances present in human milk, but not in infant formulas and (b) substances not present or not generally present in human milk. For the reasons outlined earlier, I do not consider the fact that a compound is present in human milk a reason sufficient in itself to exclude the need for clinical testing. Because there is absolutely no way to assess the safety or efficacy of such novel substances in humans without a human study, a necessary criterion in such instances is that a clinical study, with growth as one necessary end points, is indicated. Also for the reasons outlined above, other primary end point(s) must be chosen to test and properly reflect the presumed benefit of the compound added.

Criterion #5: All entirely new formulas require a growth study.

Because entirely new formulations, or formulations produced by new manufacturers, are subject to a variety of ingredient, processing, production or matrix-interaction variables that might affect nutrient form, content, absorption, bioavailability, or adequacy, it is essential to prove a new formula's nutritional equivalency (or superiority) with formulas whose nutritional adequacy and safety have been established by history of use. Thus, intent to market and entirely new formula is a criterion for a human infant growth study. This position coincides with the 1988 American Academy of Pediatrics Task Force recommendation (3).

Criterion #6: Alterations to infant formulas likely to affect gastrointestinal function or bioavailability require an infant growth study.

Gastrointestinal function, particularly enterocyte function, is obviously critical to the digestion, absorption and assimilation of foodstuffs. Compounds known to have effects on gastrointestinal functional characteristics must be subject to clinical studies since there are no adequate animal models of human infant gastrointestinal function. Similarly, because the net value of a nutrient to the infant is not realized until the nutrient is assimilated systemically, it appears axiomatic that addition of substances known to influence nutrient absorption and/or bioavailability must be tested in human infant studies. This consideration applies, as well, to modifications of current formulas that might affect absorption and bioavailability as, for example, modifications to milk fatty acid composition since individual fatty acids are not absorbed to the same extent depending on chain length and degree of saturation/unsaturation.

Further, both nutrient and non-nutritive components of human milk are known to interact in various ways with intestinal flora. These interactions both influence the nature of the intestinal flora and, in turn, floral responses or changes may influence nutrient bioavailability. The relationships among flora, iron, and lactoferrin are a classical example. Similarly, complex and as yet incompletely understood relationships among the nucleotides and pre- and probiotic compounds present in human milk, gastrointestinal

functions, and intestinal flora composition and action are areas of current active interest and investigation. Finally, it is very important to acknowledge that species differences in gastrointestinal flora, milk content and composition of its various non-nutritive components having biological, gastrointestinal, and gut flora activities, and the species-specific nature and action of many of these compounds make animal studies an inadequate indicator of human safety and efficacy. For these reasons, clinical studies in human infants with end-point measurements of growth are indicated prior to routine addition to formulas available commercially.

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