CLINICAL TESTING OF INFANT FORMULAS WITH RESPECT TO NUTRITIONAL SUITABILITY FOR TERM INFANTS

American Academy of Pediatrics

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In 1986 the American Academy of Pediatrics at the request of the Food and Drug Administration convened a Task Force on Clinical Testing of Infant Formulas. The Task Force was asked to recommend types of clinical studies to be performed before marketing to assure nutritional safety and suitability of formulas for healthy term infants. The Task Force met on two occasions, once in November 1986 and again in February 1987. Thereafter, the Committee communicated by mail and telephone and developed a report.

In the context of current regulations affecting the formula industry, and the safety record of the industry, the Task Force has attempted (1) to identify the types of clinical studies that may be useful in premarketing evaluation of infant formulas, (2) to identify the circumstances that warrant clinical testing, and (3) to match each of these circumstances with the relevant clinical studies.

Infant Formula Regulations

After extensive review of regulations governing composition and labeling of foods for special dietary uses, the Food and Drug Administration (FDA) in 1971 published regulations relating to the manufacturing and marketing of infant formula. [1] The minimum concentrations of vitamins and minerals stipulated by the FDA were largely those recommended by the Committee on Nutrition. [2] The Committee on Nutrition revised and extended its recommendations in 1976. [3]

An amendment (PL 96:359) to the Food, Drug and Cosmetic Act, referred to as the Infant Formula Act of 1980, gave FDA authority to establish quality-control procedures for infant formula manufacturing, to establish recall procedures, to establish and subsequently to revise if necessary nutrient levels, and to regulate labeling. A task force of the American Academy of Pediatrics submitted revised recommendations on nutrient content of infant formulas to the FDA in 1983. [4]

The final rule, published by the FDA in 1985, [5] specifies minimum concentration of 29 nutrients (units per 100 kcal) and maximum concentrations of 9 of these nutrients. In addition, quality-control procedures require manufacturers to analyze each batch of formula before marketing to assure that nutrient concentrations meet specifications, to test representative samples for stability over the period of shelf-life of the product, to code containers to identify the batch, and to make all associated records available to FDA investigators. In January 1986 labeling rules for infant formulas became effective. [6] These required that nutrient information be displayed in a standard tabular format and that directions for preparation and use be included. In 1987 the FDA published rules [7] concerning recall of batches of infant formulas found to be in violation of the stipulations of the Infant Formula Act. These rules require the manufacturer to act immediately to recall any violative infant formula, extending to and including the retail level.

The FDA has not published rules and regulations relating to clinical studies.

Safety Record of Formula Industry

In the opinion of the Task Force, the safety record of the infant formula industry, although not unblemished, has been remarkably good. During the past 40 years, well over 100 million infants in the United States have been fed commercially

prepared formulas. These formulas have generally been fed for the least several months, and, in a high percentage of instances, have been fed during the early months of life, when formula often serves as the sole source of nutrients and when the infant is known to be most vulnerable to development of nutritional deficiency disorders. Nutritional problems have been uncommon.

Before the 1971 publication of the FDA rule that specified minimum vitamin and mineral concentrations for infants formulas, a number of cases of nutritional deficiency disorders involving vitamin A, vitamin K, thiamin, folic acid/vitamin C, pyridoxine and iodine were reported. These reports have been reviewed by Fomon [8] and by Anderson, et al. [9]

Since 1971, there have been two instances in which an essential nutrient was omitted in commercial preparation of a formula. The inadequate provision of chloride in the manufacture of the product, Neo-Mull-Soy, resulted in a number of cases of metabolic alkalosis in 1979 and 1980. [9] It was largely in response to this problem that the U.S. Congress passed the Infant Formula Act of 1980.

A second problem concerned the omission in 1982 of pyridoxine from the product, Nursoy. This omission was detected by the manufacturer soon after the batches in question were distributed, and the products in questions (concentrated liquid and ready-to-feed) were then recalled. [10]

In both of these instances, the formula in question had been marketed for a number of years before the nutrient-deficient formula was produced. Thus, clinical studies would not have been useful in avoiding the problem or potential problem. Moreover, compliance with the current requirements for assurance of nutrient content of each batch of formula before it is released for sale should prevent recurrence of such problems.

What can be Expected of Clinical Studies?

Clinical studies are needed in some instances to supplement laboratory studies and studies with animal models. Laboratory analyses will establish that adequate quantities of all essential nutrients are present in the formula. The major roles of animal models are in establishing the safety of formula ingredients and in providing one measure of protein quality - - the protein efficiency ration (PER). In some instances, animal models may also be useful in exploring the possibility of adverse interactions between nutrients. Clinical testing is primarily useful for determining (1) acceptability of the formula, (2) ability of the formula to support normal growth, and (3) availability of selected nutrients.

As will be discussed (see OTHER MINERAL BALANCE STUDIES), adverse interactions affecting mineral absorption may, at times, be detected by metabolic balance studies. However, the Task Force is concerned that a false sense of security may arise from results of balance studies that fail to disclose evidence of adverse interactions. Thus, the Task Force believes that primary reliance should be placed on stipulations regarding minimum and maximum permissible levels of nutrients in infant formulas. These levels should be set in a manner that will avoid the likelihood of adverse interactions.

Context of Task Force Recommendations

The Task Force recommendations for clinical testing of infant formulas concern formulas available to the public. There is need to maintain great flexibility in provision of special formulas for institutional use under direct medical supervision. For example, the Task Force recommendation concerning energy density of formulas is meant to apply to generally available formulas, and should not interfere with the ability of manufacturers to supply other formulas to hospitals for use under direct medical supervision.

Types of Clinical Studies

Types of clinical studies that might be considered for evaluation of nutritional suitability of a formula for normal term infants are identified and briefly discussed in the following paragraphs. For various reasons that will be mentioned, the Task Force concludes that several of these approaches are not useful or are important to carry out only in a few quite restricted circumstances.

ACCEPTANCE/TOLERANCE STUDIES: Studies referred to as "acceptance" or "tolerance" studies are commonly carried out to obtain the appraisal of parents and physicians concerning the infant's willingness to consume the product and to tolerate it with minimal gastroenteric, respiratory or dermatologic manifestations. In practice, particular attention is generally paid to reports of fussiness, colic, cramps, regurgitation, and stool characteristics. Such studies are important to the formula manufacturer because sales of a formula will almost certainly be poor if feeding of the formula results in objectionable behavior or stool characteristics. However, if alterations in infant behavior or stool characteristics are not associated with decreased weight gain, they are unlikely to constitute a health threat. Acceptance studies will therefore contribute little to the safety evaluation of the infant formulas.

GAINS IN WEIGHT AND LENGTH: Determination of rate of gain in weight is the single most valuable component of the clinical evaluation of an infant formula. The Task Force recommends, that weight gain be determined over an interval of 3 to 4 months, beginning no later than 1 month of age. Measurements of weight should be made within well-defined age intervals, and should include an initial weight (e.g., at 14 days $\pm$ days), a final weight (e.g., at 120 $\pm$ 4 days) and a weight at some intermediate age (e.g., 60 $\pm$ 4 days). Gains in weight of each infant should then be recorded as g/day between the actual ages of measurement. Because nutrient requirements are greatest during the first 8 weeks of life, weight gain during this interval should be examined as well as for the entire 3 to 4 months of study.

Scales should be calibrated at the beginning of the study and at intervals of approximately 4 months while the study is in progress. More than one group of investigators may collaborate in accumulating the data on weight gain so long as a single protocol is followed and the collaborating units each provide data on equal numbers of infants in the experimental and control groups.

Observations of 720 infants fed milk-based or isolated soy protein-based formulas and of 419 breast-fed infants indicated that the sex-related difference in rate of gain in weight from 8 to 112 days of age was 4.7 g/day for formula-fed infants

and 3.6 g/day for breast-fed infants. [11] The difference in rate of gain between formula-fed and breast-fed infants during this age interval was 2.4 g/day for males and 1.3 g/day for females. On this basis, the Task Force recommends that a feeding-related difference in weight gain of more than 3 g/day over a 3 to 4 month period (although it is less than the sex-related difference) should be considered nutritionally significant.

The data of Nelson, et al [11] may be used as reference data under circumstances in which the study population is recruited from white, middle income, well-educated families. Similarly, other published data may be suitable as controls for specific study groups. However, under most circumstances, it will be necessary to enroll a control group of subjects fed a commercially available formula.

The standard deviation of gain in weight on sex-specific and formula-specific basis for a 3-1/2 –month interval beginning during the first month of life is about 4.5 g/day. [12] The number of subjects of a specified sex needed in each of two groups to detect a 3 g/day difference in weight gain ($p < 0.05$) with a power of 0.8 in a one-tailed test is therefore 28. [13] If both sexes are studied, it will, of course, be necessary to take into account the sex-related difference in rate of gain.

The Task Force considers it unlikely that a significant difference in length gain between an experimental and control group will be demonstrated in the absence of significant difference in weight gain. For this reason, data on length gain are not considered essential in clinical testing of infant formulas. In addition, the requirement that two trained individuals be available for each measurement of length [8] is difficult to meet. The Task Force believes that mandating measurements of length would be likely to result in accumulation of data without adequate quality control.

Although it seems possible that change in head circumference may serve as a surrogate for change in length, [14] there is no evidence to suggest that change in head circumference will be useful in detecting the small differences in growth rate needed for clinical testing of infant formulas.

FOOD INTAKE: In a few centers, it is feasible to measure formula consumption over observation intervals of weeks or months. If such determinations of formulas intake are combined with well-controlled measurements of weight, gain in weight per unit of energy intake can be determined during age-specific intervals of observation. In the case of infants fed formulas that comply with provisions of the Infant Formula Act, low gain in weight per unit of energy intake suggests low availability of energy sources, usually fat.

Such studies are labor intensive and are unlikely to be feasible with the number of subjects needed to detect a small but nutritionally significant difference in weight gain between an experimental group and a control group. The Task Force considers the major usefulness of the approach to be in early clinical evaluation of formulas that include major ingredients not previously used in infant formulas (e.g., a new source of protein). Thus, in some instances, intensive study of relatively few infants may be desirable before undertaking acceptance/tolerance studies or studies of weight gain with larger groups of infants under less meticulously controlled circumstances.

BODY COMPOSITION: Normal growth implies appropriate composition of the increment in body weight. Sequential measurements of various aspects of body composition (e.g., body water, body fat, bone mineral) have the potential of defining changes in body composition. However, in the opinion of the Task Force, such measurements have not yet reached the stage of precision, non-invasiveness and convenience that would make them feasible as a part of routine clinical testing of infant formulas.

SERUM CHEMICAL INDICES: Indices of protein adequacy of the diet. For reasons that are not well understood, serum concentration of albumin appears to be of rather limited usefulness in assessing protein-energy malnutrition. [15-18] On the other hand, this determination has been shown to be useful in evaluating protein adequacy of the diet in adult subjects [19] and infants. [20-24] Serum concentrations of albumin demonstrate predictable increases in normal infants during the early months of life. [23, 24] Lesser increases in concentration may reflect inadequacy of the diet. When concentration of albumin is to be determined, the Task Force recommends that blood be obtained at a specified age ($\pm$ 4 days), preferably between 90 and 120 days of age in both experimental and control groups. The control group should be fed a commercially available formula and infants in experimental and control groups should be enrolled during the first month of life. There does not appear to be a significant sex-related difference in serum albumin concentration of infants.

In studies of normal infants fed conventional milk-based formulas or minor modifications of such formulas, serum concentrations of albumin at ages 56, 84 and 112 days of age were 4.00, 4.16 and 4.25 g/dl (standard deviations 0.28, 0.24 and 0.26 g/dl, respectively). [24] Thus, to demonstrate a difference of 0.25 g/dl between experimental and control groups ($p < 0.05$, power 0.80) in a one-tailed test will require about 30 infants, 15 in each group.

Serum concentration of urea nitrogen is a useful index of protein adequacy of the diet when two diets, one adequate and the other inadequate in protein quality, are fed to provide the same nitrogen intakes. [24, 25] Under these conditions, serum concentration of urea nitrogen will be greater when the poorer quality protein is fed. Because FDA regulations specify minimum quantity and quality of protein in infant formulas, [5] the Task Force concludes that this test of protein quality is unnecessary.

A number of reports [26-35] suggest that retinol-binding protein, thyroxin-binding prealbumin and transferrin may also be useful as indices of protein nutritional status. In the opinion of the Task Force, the usefulness of these tests for evaluation of protein adequacy of the diet has not been convincingly demonstrated. If the value of these indices becomes established, they should be included in evaluation of the protein adequacy of the diet.

Similarly, postprandial plasma concentrations of amino acids have been explored in adult subjects [36-39] and in infants [40] as an index of the protein adequacy of the diet. Studies have also been carried out to compare postprandial plasma concentrations of amino acids by breast-fed infants and infants fed various formulas. [41, 42] However, the significance of plasma amino acids profiles that differ from those of breastfed infants is uncertain. For this reason, the Task Force does

not recommend that such determinations be required in evaluation of infant formulas.

Indices of iron nutritional status. In evaluating iron nutritional status, at least three indices should be used. [43] Those of most value in infancy are serum concentration of ferritin, saturation of transferrin, erythrocyte protoporphyrin and mean corpuscular volume.

Indices of nutritional adequacy of the diet with respect to minerals other than iron. Serum concentration of inorganic phosphorus may be low and activity of alkaline phosphase high when the diet is inadequate in calcium or phosphorus. [44-48] Because serum concentrations of phosphorus vary with age and diet, [49] it will be necessary to include a control formula (a marketed formula with the same or similar sources of protein, fat and carbohydrate) in the clinical studies. Differences in serum concentrations of phosphorus without significant elevations of alkaline phosphatase activity are unlikely to be nutritionally significant. Therefore, the number of subjects in experimental and control groups should be based on the variability of alkaline phosphatase activity at the specified age.

Although serum concentrations of various essential minerals are usually abnormally low in cases of overt deficiency (e.g., zinc cooper, selenium deficiency), serum concentrations of most minerals appear to be little affected by subclinical deficiency, and have not been shown to be useful in assessing dietary adequacy. However, the Task Force cannot exclude the possibility that under well-defined experimental conditions the serum concentration of a mineral may be useful in judging the adequacy of the diet. If, in the future, such experimental conditions can be defined, clinical testing should include determination of serum concentrations.

More promising for assessing dietary adequacy are determinations of activity of various mineral-dependent enzymes. Research in this area is progressing rapidly and it seems likely that such determinations may prove to be useful in identifying adverse nutrient interactions. Thus, decrease in erythrocyte superoxide dismutase activity may reflect interference with availability of copper, [50] and low activity of serum and/or erythrocyte glutathione peroxidase may reflect interference with availability of selenium. [51] The Task Force believes that development of sensitive methods for detecting adverse nutrient interactions involving minerals is of high priority for future recommendations of clinical testing of infant formulas.

Serum lipids. Although serum concentrations of lipids and lipoproteins reflect the lipid composition of the infant's diet, there is currently no adequate basis for determining what lipid profiles are desirable for the infant. The Task Force therefore believes that such determinations are currently of little use in evaluation of formula adequacy.

METABOLIC BALANCE STUDIES: Use of metabolic balance studies for evaluation of the adequacy of infant formulas introduces serious practical problems. Few centers have access either to normal infant subjects or to infants during the late stages of recovery from malnutrition. In addition, the studies are difficult to perform, labor-intensive and expensive. It is therefore particularly important to use balance studies only to obtain information that cannot be obtained by other approaches.

Proper use of balance studies requires that the formula to be evaluated be compared with a control formula in cross-over studies with the same infants or with two well-matched groups of infants. It is essential for interpretation of the results that intakes of the nutrient in question (e.g., fat, calcium) be similar from both formulas.

Nitrogen balance. When the same intakes of nitrogen are fed in the form of proteins of different quality, nitrogen balance may be greater with the protein of higher quality. [52, 20, 24] However, the difference in protein quality between the two diets must be greater than would be possible under current regulations regarding quantity and quality of protein in infant formulas. [5] Results of nitrogen balance studies in which intakes of nitrogen differ between experimental and control groups are virtually impossible to interpret. For these reasons the Task Force does not recommend nitrogen balance studies for evaluation of the protein or amino acid adequacy of the diet.

Fat balance. Normal, term infants fed various mixtures of the fats currently used in infant formulas in the U.S. rarely excrete more than 15% of fat intake. [53-56] Such excretions of fat are compatible with satisfactory energy balance by infants fed ad libitum. Because little is known about losses of micronutrients under conditions of high fat excretion, and because fat retention of 85% or more is readily achievable, the Task Force considers lesser retention undesirable.

Under most circumstances, cross-over studies comparing fat excretion of infants fed at one time the formula with the new fat mixture and at another time a similar formula with the fat mixture of a currently marketed formula will be desirable. The variance in excretion of fat by infants fed the actual mixtures of fat now in use in commercially available formulas is generally less than 5%. Thus, a cross-over study with 6 infants is likely to be adequate. Fat balance studies should generally be of 72 hours duration or longer, and the method used for determination of fecal fact content should be appropriate for the type of fat in the diet.

Because fat balance studies do not require collection of urine, it may be possible to carry out such studies in the home. Investigators proposing to use this approach will need to provide data on the variability of fat excretion with conventional formulas.

Calcium and phosphorus balance studies. Calcium and phosphorus balance studies are useful in evaluation of infant formulas. Unsatisfactory phosphorus balance will rarely occur under circumstances in which calcium balance is satisfactory. Therefore, in most instances the desirable sample size should be based on calcium balance considerations.

Between-subject variability in calcium absorption is appreciably greater than within subject variability. For example, standard deviations in absorption of calcium from three formulas determined in 72-hour balance studies by DeVizia, et al [55] were 10, 11 and 10% of intake, respectively, whereas the corresponding within-subject standard deviations were about 8%. [12] Thus, with a cross-over design in which each of 6 infants receives each of two feedings, it will be possible to detect ($p < 0.05$, power 0.8) a difference in absorption of 10% of intake. [57] If fecal markers are not used, balance studies may need to be of more than 72 hours duration.

Cross-over studies carried out at two-week intervals (i.e., at least an 11-day adaptation period between 72-hour balance studies) appear to be adequate when concentrations of calcium and phosphorus are similar in the two formulas. If the concentrations of calcium or phosphorus are dissimilar in the formula to be tested and the control formula, the desirable duration of the equilibration period will need to be determined.

Other mineral balance studies. Although balance studies are potentially useful in detecting interactions that adversely affect absorption of various trace minerals, the Task Force believes that such interactions can be avoided in nearly all instances by regulations that stipulate minimum and maximum concentrations of nutrients in infant formulas. Trace mineral balance studies will therefore rarely be useful for formula evaluation.

Bone mineral content. Over the past decade great advances have been made in refinements of techniques for determining bone density. In the opinion of the Task Force, these methods have not yet reached a stage at which they are useful in evaluating the mineral adequacy of an infant formula. However, the approach offers considerable promise for the future.

Circumstances that Warrant Clinical Testing

Both new formulas and various changes or modifications of previously approved formulas warrant clinical testing.

NEW FORMULA: The Task Force considers any formula introduced by a manufacturer who is not already marketing a formula in the United States to be a "new" formula. This classification applies even if the formula is commercially available in other countries. However, clinical testing of the formula in another country may, in some instances, fulfill the U.S. requirements for clinical testing.

In the case of formulas produced by U.S. formula manufacturers, the Task Force concluded that there was no advantage in distinguishing between a new formula and a modification of an existing formula. The requirements for testing of formula modifications are similar in all relevant respects to those for testing new formulas. The only difference is that a formula modification does not require testing of the formula components that are unchanged.

As may be seen from the table, a new formula requires clinical testing of weight gain, serum chemical indices, and balance studies.

ENERGY CONCENTRATION LESS THAN 63 kcal/dl OR MORE THAN 71 kcal/dl: Formulas providing less than 63 kcal/dl or more than 71 kcal/dl require study of weight gain (Table). Formulas providing more than 71 kcal/dl may also warrant testing for urinary solute concentration under various circumstances of feeding (e.g., in a hot, dry environment).

NEW ENERGY SOURCE: Introduction of a new source of protein, fat, or carbohydrate in a formula will generally warrant study of weight gain. In the case of a new source of protein, serum concentration of albumin should also be determined. In the case of a new source of fat, fat balance studies will be desirable.

PROTEIN LESS THAN 2 g/100 kcal: A formula providing less than 2 g of protein per 100 kcal warrants study of weight gain and determination of serum concentration of albumin.

CHANGE IN PROTEIN MIXTURE: Currently marketed formulas in some instances provide protein from two sources – non-fat cow milk and cow milk whey proteins, or non-fat cow milk and isolated soy protein. In the future, other formulas providing two or more sources of protein may be marketed. In the opinion of the Task Force, mixture of non-fat cow milk and cow milk whey proteins have been well studied and may be considered interchangeable. When other mixtures of proteins are involved, a study of gain in weight should be carried out if the proportion of protein provided from a specified source is changed by more than 10%. This requirement should apply whether the change is made at one time or in two or more steps.

CHANGE IN FAT MIXTURE: The Task Force considers a major change in proportions of energy supplied by various fat sources to be as important as introduction of a new source of fat. Thus, if the proportion of energy from a particular fat is increased from less than 30% to more than 50%, or from less than 60% to more than 80%, fat balance studies should be carried out.

CHANGE IN SOURCE OF CALCIUM AND/OR PHOSPHORUS: If the source of calcium and/or phosphorus in a formula is changed, the effect on serum concentrations of phosphorus and alkaline phosphatase should be determined and calcium and phosphorus balance studies should be carried out.

IRON CONCENTRATION MORE THAN 1.0 mg/100 kcal BUT LESS THAN 1.8 mg./100 kcal: According to FDA regulations, [6] a formula will carry the statement "Infant Formula With Iron" or a similar statement if the formula provides 1 mg or more of iron per 100 kcal. Formulas providing 1.8 mg of iron per 100 kcal have been demonstrated to meet iron needs of infants. [58-60] Few data are available concerning the effectiveness of formulas fortified at lower levels, Thus, clinical testing should be required before marketing to demonstrate the effectiveness of a lesser concentration of iron in meeting iron needs.

In the future, if it is demonstrated that iron concentration of 1 mg of iron per 100 kcal is as satisfactory as 1.8 mg of iron per 100 kcal in meeting iron needs of infants, the requirement for clinical testing can be eliminated. If some intermediate level of fortification (e.g., 1.4 mg of iron per 100 kcal) but not 1.0 mg of iron per 100 kcal is adequate, the labeling regulation should be changed, thus eliminating the need for clinical testing.

Based on the results of the study by Hertrampf, et al [60] concerning indices of iron nutritional status of breast-fed infants and of infants fed iron-fortified formulas, a study of 100 infants, 50 fed the formula providing less than 1.8 mg of iron per 100 kcal and 50 fed a control formula (1.8 mg/100 kcal) is likely to be adequate. The infants should be no older than 3 months at the time of enrollment and the study should be terminated when the infants are no less than 12 months of age. Indices of iron-nutritional status should be determined at approximately 3 months of age and at the conclusion of the study. Interpretation of the results should be based on comparison of the two groups with respect to number of subjects exhibiting two or more abnormal indices of iron nutritional status.

Alternatively, it may be feasible to compare erythrocyte incorporation of iron isotopes after standardized feeding of the formula in question and a control formula providing 1.8 mg of iron per 100 kcal.

CHANGE IN SOURCE OF IRON: Formulas currently marketed in the United States are fortified with ferrous sulfate. If other sources of iron are to be used, efficacy should be demonstrated in the manner described for changes in concentrations of iron.

ADVERSE REACTIONS: During clinical testing of any type, meticulous records regarding adverse reactions should be maintained and made available to the FDA.

Changes in Formulation and Processing That Will Generally not Warrant Clinical Testing

As suggested in the previous section, changes in energy concentration do not require clinical testing if the final energy concentration is at least 63 kcal/dl and no more than 71 kcal/dl. Within the limits specified by the FDA rule, changes in percentages of energy supplied by fat and carbohydrate do not require clinical testing. With the exception of the rather large changes in proportions of fat mentioned previously (see CHANGE IN FAT MIXTURE), clinical testing is not required when changes are made in the proportions of fat provided from various sources or in the proportions of carbohydrate provided from various sources. Changes in protein concentration do not require clinical testing if one the final protein concentration is at least 2 g/100 kcal and does not exceed the limit specified by the FDA rule (currently 4.5 g/100 kcal). Clinical testing is not required for changes in proportions of protein supplied by non-fat cow milk and cow milk whey proteins or for changes of less than 10% in the proportion of protein supplied by other sources. Increases in iron concentrations between 0.2 and 1.0 mg/100 kcal or between 1.8 mg/100 kcal and the upper limit permitted by the FDA rule (3.0 mg/100 kcal) do not require clinical testing.

The Task Force recommends that maximum concentrations of minerals (in fact, of all nutrients) be specified for infant formulas. As already suggested in relation to metabolic balance studies, if this is done, the maximum concentration of each mineral will presumably be set at a level that will avoid adverse interactions with other minerals, including any mineral present at the minimum level. In establishing maximum permissible concentrations of nutrients in infant formulas, exceptions should be made with respect to nutrients of low bioavailability (e.g., a portion of the phosphorus and, perhaps, the iron of formulas containing isolated soy protein).

The major hazard from vitamin toxicity relates to vitamins A and D, and the FDA rule specifies maximum concentrations for these vitamins in infant formulas. The Task Force does not believe that clinical testing will be useful in detecting toxicity from these or other vitamins. Vitamin deficiency will be prevented by the specified minimum levels of vitamins. Therefore, changes in vitamin concentrations do not warrant clinical testing.

Implementation of Guidelines on Clinical Testing of Infant Formulas

The rather specific nature of the Task Force recommendations should not imply a desirability for rigidity in implementation. Alternative approaches to obtaining the needed information should be encouraged. Additional clinical testing will sometimes be desirable to cover circumstances not considered by the Task Force. On the other hand, the FDA will undoubtedly waive the requirement for

clinical testing in the case of certain proposed changes in formula composition. As an example, FDA might waive the requirement for clinical testing of a new source of energy if the ingredient in question was generally recognized as safe (GRAS), was to serve as a stabilizer and would provide only a few percent of energy intake. A case by case consideration of each proposed change will be necessary. The FDA may wish to consult with extramural scientists before making certain of these decisions. However, whatever mechanism is developed for obtaining such consultation should be convenient for the FDA and expeditious for the formula industry.

The recommendations presented in this report are based primarily on the use of currently available methods of formula testing as applied to formulas similar to those marketed in the United States. As new or improved approaches to clinical testing of formulas are developed, these recommendations will need to be modified. For example, in the future, studies of growth may include changes in body composition; the adequacy of the nitrogenous component of the diet may be determined by stable isotopic studies of amino acid oxidation; availability of minerals may be evaluated by determining change in bone density or by determining true absorption (with the use of a stable isotope).

Moreover, the formula manufacturers have reached a level of technologic sophistication that may permit the development of new formulas quite unlike those that are now commercially available. Such formulas will warrant special consideration concerning clinical testing.

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PROPOSED CLINICAL TESTING

	Gain in Weight	Selected Serum Chemical Indices	Balance Studies: Fat	Balance Studies: Calcium and Phosphorus
New formula	X	X	X	X
Energy concentration < 63 or > 71 kcal/dl	X			
New energy source		X		
protein	X			
fat	X		X	
carbohydrate	X			
Protein < 2g/100 kcal	X	X		
Change in protein mixture	X			
Change in fat mixture			X	
Change in source of calcium and/or phosphorus		X		X
Iron concentration > 1.0 and < 1.8mg/100 kcal*		X		
Change in source of iron*		X		

*Requires comparison of proposed new formula and currently marketed formula (1.8 mg Fe/100 kcal) with respect to indices of iron nutritional status (see text).

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