"bioavailability" and of "healthy growth."

The concept of "healthy growth" was discussed in the report of the House Committee on Interstate and Foreign Commerce that accompanied the 1980 act. The report states that infant formulas are often the sole source of nutrition for infants, and that "the growth of infants during the first few months of life often determines the pattern of development and quality of health in adult life" (Ref. 5). FDA considers the concept of "healthy growth" to be broad, encompassing all aspects of physical growth and normal maturational development, including maturation of organ systems and achievement of normal functional development of motor, neurocognitive, and immune systems. All of these growth and maturational developmental processes are major determinants of an infant's ability to achieve his/her biological potential, and all can be affected by the nutritional status of an infant.

"Bioavailability" of a nutrient for an infant means that the nutrient is physiologically available in sufficient quantities to perform its metabolic functions (Ref. 55). In a formula product, bioavailability of individual nutrients is affected by the net effect of the formulation and processing of the product on the chemical form of the nutrient. These processes are influenced by such factors as the chemical form of the nutrient in the ingredient source, the chemical form of the nutrient after processing, and the net effect of various inhibitors and enhancers in a food or meal on the chemical form of the nutrient and its ability to be absorbed and utilized by the infant. In the infant, the bioavailability of a nutrient is determined by the net effect of the amount of nutrient that is converted during digestion to an absorbable form, the proportion of the nutrient that is absorbed into the bloodstream, the proportion of the absorbed nutrient that is converted to its biologically useful form, and the proportion that is lost through excretory processes (Ref. 55). Bioavailability varies among nutrients within a given food product and, for a given nutrient, among foods. The factors affecting nutrient bioavailability are complex and can be difficult to predict based on analyzed nutrient values alone.

Bioavailability issues are particularly critical for infants during the first few months of life, where a single food (infant formula) serves as the sole source of all nutrients at a period when rapid physical growth and development and maturation of various organ systems makes the infant particularly vulnerable to harm by nutritional insults. Unlike the mixed diet of persons beyond infancy where poor bioavailability in one food can be compensated for by other foods in the diet, a problem with bioavailability in an infant formula affects the total amount of nutrient available to that infant for several months after birth. Furthermore, requirements for nutrients are higher per kilogram body weight during early infancy than at any other time during the life cycle. Because numerous critical developmental milestones (e.g., neurocognitive or immune functions) must be achieved by young infants, a nutrient insufficiency during infancy can quickly develop into serious, and in some cases, permanent adverse effects on a range of developmental processes, including physical growth and organ maturation. Thus, a problem with bioavailability is far more critical for a food such as infant formula than it is for foods that are used as part of a mixed diet by the general population.

Furthermore, the rapidly changing and increasingly complex physical, chemical, and biologically significant characteristics of ingredients used in new and reformulated infant formulas make it important to continually ensure that quality factor requirements are met. Changes in formulation of infant formulas are made by manufacturers for a variety of reasons, including enhancing the functional characteristics of the formula (e.g., to prevent separation of ingredients or to prevent clumping that will plug nipples on bottles), to enhance digestibility of the formula (e.g., different sources or blends of fats), or to improve the nutritional quality (e.g., a different source of protein or of a vitamin or mineral, or adding a nonrequired nutrient such as selenium). For example, in some formulas, novel sources of vegetable oils (e.g., fractions of plant oils that are particularly rich in certain types of fatty acids) have partially or fully replaced cow's milk fat as the fat source (Refs. 56 and 57). Whey proteins or highly processed proteins (e.g., hydrolyzed proteins) are now frequently used as partial or complete replacements for more traditional cow's milk protein sources. In other cases, nutrient/nutrient interactions (e.g., high iron inhibiting absorption of zinc) or nutrient/ingredient interactions (e.g., phytates from soy protein isolates inhibiting absorption of zinc, or the replacing of the milk sugar (lactose) that enhances absorption of calcium with a sugar source that does not have this ability) can adversely affect nutrient availability.

New processing methods may also have unintended consequences when used with established ingredients or formulations. For example, a new processing method that subjects the formula to conditions that are less denaturing to cow's milk proteins than traditional heat treatments could produce a formula that is less digestible and that causes reactivity of the gastrointestinal wall, such as has been seen with whole cow's milk (Ref. 58).

In summary, consideration of quality factors goes beyond analytical measures of the presence or absence of a nutrient in the formula product and is needed to provide assurance that adverse effects on the nutritional value of the formula for the infant do not unintentionally or unknowingly occur as a result of the formulation or the processing of an infant formula. Chemical analysis of the formula product to define its nutrient composition often overestimates the amount of nutrient that is bioavailable for physiological use by the infant. The quality factors, therefore, provide a means of evaluating whether a nutrient has become less bioavailable than would be expected, so that it is not sufficiently effective to meet its normal nutritive functions, or whether its bioavailability has been enhanced to a level that raises safety concerns.

Quality factor requirements are distinctly different from quality control procedures. While "quality control procedures are intended to insure that the safety and nutritional potency of a formula is built into the manufacturing process" (Ref. 5), quality factors are intended to ensure that an infant formula contains an adequate amount of each nutrient in a form that can be digested, absorbed, and utilized so that the infant's physiological needs for these nutrients will be met (Ref. 5). Changes in ingredient sources and processing can affect the chemical forms of nutrients in the formula product. Such changes can affect the digestion and absorption of food nutrients such that: (1) Absorption is incomplete, (2) absorbed nutrients are not in a form that allows use by metabolic pathways, or (3) the nutrient may interact with other dietary substances to cause excessive excretion. Thus, the amount of nutrients (i.e., the analyzable amounts) in formulas must generally be higher than the physiological requirements of infants (i.e., the amounts of nutrients needed by the body to meet metabolic and growth needs of infants). Although these inefficiencies are generally taken into account when recommending nutrient levels for infant formulas, there

is always the potential for affecting nutrient bioavailabilities in unexpected ways.

In summary, a demonstration that both the quantitative and quality factor requirements for essential nutrients in an infant formula are met is necessary to ensure that the infant formula is likely to meet all of the known physiological nutritional needs of infants and to ensure that healthy growth and nutritional well-being will be achieved by an infant consuming the infant formula as the sole source of nutrition.

2. Identification of Quality Factors

In testimony before the passage of the 1986 amendments, the agency informed the Senate that the state of knowledge and science with respect to quality factors was still evolving, and that, therefore, there was a basis for only one quality factor for a nutrient. (Although the testimony to the Senate does not specify the identity of the nutrient for which there was a basis for a quality factor, the quality factor was the protein efficiency ratio used for assessing protein quality (Ref. 1).) Senator Metzenbaum stressed that the amendments contemplated that additional quality factors would emerge, and that the Secretary should implement requirements for such factors as quickly as scientific advances would allow.

The agency subsequently took a major step toward establishing quality factors through a contract in 1986 with the CON/AAP. The AAP earlier had published recommendations regarding the quantities of nutrients needed in infant formulas (Ref. 59). These recommendations were relied upon during the development of the nutrient specifications of the act (Ref. 60). In its report to FDA, "Clinical Testing of Infant Formulas with Respect to Nutritional Suitability for Term Infants" (Ref. 6), the CON/AAP identified those conditions in which changes in formula composition warranted clinical testing. The CON/AAP stated that "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." The CON/AAP also discussed the limitations of the available measurements, providing an assessment of the limits of scientific knowledge.

The agency has considered the CON/AAP report carefully and has also considered new scientific information published since the release of that report to determine what quality factors are appropriate for nutrients in infant formula. Based on its consideration, FDA is proposing to adopt § 106.96. This section, if adopted, will require that all infant formula be of sufficient quality that it meets the nutritional requirements of infants for healthy growth when fed as the sole source of nutrition, as indicated by a general quality factor for physical growth, assessed using anthropometric measures of infants consuming the formula, and by a nutrient-specific quality factor for protein biological quality, assessed by an animal bioassay using the formula.

The agency is not proposing to require that manufacturers measure, individually, the absorption, metabolism, metabolic transformation, or utilization of any of the other essential nutrients. These measures are often technically difficult or unavailable, difficult to interpret, or invasive, thus causing unnecessary testing of infants without potential for providing meaningful results. Rather, the agency has tentatively concluded that current scientific knowledge and ethical and practical considerations are supportive only of requiring two quality factor measures: (1) Physical growth of infants consuming the formula as an integrative indicator of the net effect of the overall nutritional quality of the formula, and (2) a rat bioassay of protein quality in the formula product to ensure that the infant's needs for individual amino acids will be met.

The agency has tentatively determined that these are minimum requirements. The agency recognizes that, on a case-by-case basis as warranted by the formulation and intended use of a particular infant formula, demonstration of additional quality factors may be necessary. For example, a formula intended for use by premature infants who are at a particularly vulnerable developmental stage relative to nutritional needs to support neurocognitive development may need to be subject to testing that includes measurement of this endpoint to ensure that the formula supports healthy growth. In addition, a formula in which a novel fatty acid has been added to enhance the formula's ability to meet nutritional needs for supporting visual development may need to be evaluated to determine whether it has adverse nutritional effects on other aspects of healthy growth (e.g., on development of immune function).

3. The Regulation

Proposed § 106.96(a) sets forth quality factor requirements that reflect the minimum measures needed to evaluate the nutritional quality of an infant formula product, taking into account current scientific knowledge and the usefulness of the outcome measures for evaluating quality factors, while minimizing unnecessary testing of infants serving as subjects in clinical trials. Infant formula is defined in the act as a complete or partial substitute for human milk (section 201(aa) of the act). Obviously, the greatest need for a nutritionally complete formula that meets all quality factors is when the formula is used as a complete substitute for human milk. When no other form of nutriture is available to the infant, the formula must provide all of the nutrients needed for the healthy growth of the infant. There is no room for error or miscalculation. The absence or an inadequate level of an essential nutrient will be evidenced by growth failure and other signs or symptoms resulting from nutritional insufficiencies. FDA has tentatively concluded, therefore, that an evaluation of the ability of a formula to support healthy growth must be made under its most demanding conditions of use, i.e., when it is used as the sole source of nutrition, because other foods may mask or compensate for deficiencies in the formula that would occur if the formula were used as a complete substitute for human milk, which would produce results that cannot be meaningfully interpreted.

Proposed § 106.96(b) identifies "normal physical growth" as a quality factor. This quality factor reflects the CON/AAP recommendation that the determination of physical growth rate is the most valuable component of the clinical evaluation of an infant formula (Ref. 6). Physical measures of growth such as weight gain are the most widely accepted and used markers of a young infant's overall ability to digest and utilize those nutrients provided by the formula. The very rapid rate of growth in early infancy means that abnormalities in growth rate can be detected in a few months, providing an easily measured and sensitive, although nonspecific, indication of nutritional insufficiencies (Ref. 4). Physical measures of growth rate are easily done, are familiar to both parents and health professionals, and are a normal part of routine office visits. They are noninvasive and pose little or no risk to infants and provide meaningful results for evaluating the ability of an infant formula to support physical growth in very young infants. Thus, the agency has tentatively concluded that the ability of the formula, when fed as a sole source of nutrition, to meet the nutritional requirements of young infants for normal physical growth is a

necessary indicator of the overall nutritional quality of the formula.

Proposed § 106.96(c) requires that the protein in infant formulas be of sufficient biological quality to meet the protein nutritional requirements of infants. Protein, while generally discussed as a single nutrient, depends for its nutritive value on the inclusion of all essential amino acids at levels and relative proportions needed to support healthy growth. The protein requirement is really the sum of different requirements for 10 essential amino acids that occur at different levels and proportions in various food protein sources. Protein quality is also affected by differences in digestibility of different protein sources, by factors that modify digestion, and by chemical reactions that affect the ability of enzymes in the infant's gastrointestinal tract to digest and absorb the amino acids in the protein source. Once absorbed, the relative proportions of the amino acids can affect their uptake by body tissues because of competition for receptors and transport systems. Thus, protein quality depends on a number of complex interactions and conditions that can be difficult to predict.

Chemical analysis of foods generally only measures the amount of total protein present and does not identify specific amino acids or their ability to meet the physiological needs of infants for the essential amino acids. Chemical analysis alone, therefore, is not capable of predicting whether adequate amounts of all essential amino acids are present, or whether the amino acids present are able to support healthy growth in infants. Yet ensuring that the protein in an infant formula's is of high biological value is critical to an infant's health. For example, during the first year of life, the protein content of an infant's body increases from 11 to 15 percent at the same time that the infant's body weight increases by 7 kg. The average increase in body protein is about 3.5 g/day for the first 4 months of life and about 3.1 g/day for the next 8 months. These protein requirements must be met by a formula that not only contains adequate protein but also contains protein of high biological quality in a form that can be utilized by the infant. Because biological quality varies among protein sources and may be adversely affected by processing methods and other constituents present in the formula, the agency has tentatively concluded that the biological quality of the protein in an infant formula is a necessary quality factor. This quality factor will require an evaluation of whether the formula contains the essential amino acids and total nitrogen in the amounts and proportions necessary to permit normal tissue and organ growth and development. As discussed later in this document, the agency is proposing in § 106.97(b) that the biological quality of the test protein be measured by the Protein Efficiency Ratio (PER) rat bioassay and be comparable to the biological quality of the milk protein casein.

Proposed § 106.96 does not include quality factor requirements for all nutrients required by infants because methods to determine whether these requirements are met are not available or are not practical for most nutrients (e.g., results cannot be meaningfully interpreted, or methods are invasive, thus causing unnecessary testing of infants). Nonetheless, FDA has tentatively concluded that, as the science evolves, establishing quality factor requirements for other nutrients needed by infants would provide assurance, beyond that provided by the general quality factor of physical growth in proposed § 106.96(b) and the specific protein quality factor in § 106.96(c), that a formula will meet the overall nutritional needs of infants. As the science evolves, FDA anticipates being able to progress beyond generalized, nonspecific indicators of overall nutritional intakes (e.g., measures of physical growth), to more specific and sensitive measures of biochemical and functional nutritional status. FDA also has tentatively concluded that, on a case-by-case basis, additional quality factors may be needed for a specific formula product if formulation or processing concerns raise sufficient quality factor questions such that additional measures are necessary to adequately ensure that the nutritional quality of the formula supports healthy growth. FDA asks for comment on criteria as to when such measures are required.

4. Request for Comment on Need for Establishing Requirements for Other Quality Factors

Proposed § 106.96(b) and (c) set forth minimum requirements for quality factors (physical growth and protein quality) that all infant formulas should meet. FDA has tentatively concluded that these quality factors are consistent with current state-of- the-art science and provide significant information on the nutritional quality of the infant formula without requiring unnecessary or meaningless testing of infant enrollees in studies.

As discussed above, the 1986 amendments contemplated that when scientific research identified criteria that could be used to establish quality factors for specific nutrients in infant formula, the agency would establish quality factor requirements for those nutrients. Proposed § 106.96 will establish two quality factors (physical growth and protein quality) because the agency has tentatively concluded that there is sufficient scientific evidence of the importance of these quality factors, and because adequate methods exist to meaningfully and ethically measure these factors.

However, the CON/AAP report discussed other nutrients necessary for healthy growth of infants and for which the report recommended establishing quality factor requirements (Ref. 6). The agency has studied the evidence supporting the establishment of quality factor requirements for these other nutrients, and the methods available for determining whether an infant formula meets quality factor requirements for these nutrients. FDA has tentatively concluded that establishing quality factor requirements for the three additional nutrients recommended by CON/AAP (i.e., (a) fat, as measured by fat balance; (b) calcium and phosphorus, as measured by calcium and phosphorus balance; and (c) iron as measured by iron bioavailability) is not warranted at this time. FDA, however, solicits additional information that it will consider before reaching a final decision on whether the scientific evidence and usefulness of results are sufficient to support establishing these additional quality factor requirements. Therefore, the agency requests comments and information on: (1) The scientific evidence on the importance of the amount, type, and sources of fat, calcium and phosphorus, and iron in infant formula, and (2) the appropriate methods and interpretative criteria to determine whether an infant formula meets the nutritional requirements for fat, calcium and phosphorus, and iron of infants consuming the formula as the sole source of nutrition. The basis upon which the agency is considering establishing quality factor requirements for these nutrients is discussed below.

a. *Fat.* The agency requests comment on a quality factor for fat balance that would require that all infant formulas be formulated and manufactured to provide fat in a manner that allows the fat to be absorbed and retained by infants at a level that the energy and other nutritional requirements of the infant are not adversely affected (Ref. 6). Normal, healthy, full-term infants fed various mixtures of the fats traditionally used in infant formulas in the United States rarely excrete more than 15 percent of their fat intake (Ref. 6). This level of fat excretion is an indication

that the fat is highly digestible. The use of a fat with lower digestibility would adversely affect energy balance, could reduce the absorption of fat-soluble vitamins and other nutrients, and could have a negative impact on healthy growth of the infants.

b. *Iron.* The agency solicits comment on a quality factor that would require that all infant formula be formulated and manufactured such that the iron used is bioavailable and meets the iron requirements of the growing infant. The maintenance of adequate iron status in the infant is important because iron is required to transport oxygen in the red blood cells to body tissues (as a component of hemoglobin), to supply oxygen to muscle tissue (as a component of myoglobin), and to support normal mental development. Full-term infants are generally born with adequate iron stores to meet their iron needs for the first few months of life, but the iron needs of premature infants and older infants must be met by the diet.

Iron bioavailability from infant formulas is low compared to the iron bioavailability from human milk (Refs. 61 and 62).

Nutrient sources and other ingredients, such as protein sources, can affect the chemical form of iron, thus interfering with its potential for absorption (Ref. 63). Furthermore, factors that enhance iron bioavailability from human breast milk are poorly understood and currently are not present in commercial formulas. Consequently, infant formulas are fortified with up to 10 times the amount of iron found in human milk. If, however, the bioavailability of the iron in the infant formula is substantially improved by a change in the formulation or processing of the formula, then reductions in the amounts of iron added to the infant formula may be necessary to prevent the infant from absorbing excessive amounts of iron which could be unsafe because high dietary intakes of iron can adversely interfere with the bioavailabilities of other nutrients (59 FR 51030, October 6, 1994). If, however, the iron was bound to another ingredient such that it interfered with absorption, the infant's physiological needs for iron might not be met. Infant formula iron levels and iron bioavailability, thus, represent a delicate balance between effectiveness and safety that cannot be adequately predicted by chemical analysis of the iron content of the formula, but can best be assessed by measurement of clinical indicators of iron status.

Early changes in iron nutritional status are not likely to be detected by the general quality factor of physical growth. Therefore, a quality factor requirement for an infant formula to meet the iron requirements of infants, and to contain sufficient bioavailable iron for this purpose, may be needed. The agency, however, is concerned that clinical studies, as described in proposed § 106.97(a), in which selection criteria include requirements that enrollees be healthy, full-term infants aged 0 to 4 and 5 months, may not be sensitive enough to detect significant differences in iron bioavailability of a formula product. Healthy, full-term infants are usually born with adequate iron stores to maintain normal iron status for the first 3 to 4 months of life—the period of time that a clinical trial would be conducted. Without assurance that the test results are meaningful, the agency has tentatively decided not to require a specific quality factor for iron bioavailability.

c. *Calcium and phosphorus.* The agency also requests comment on a quality factor that would require that all infant formulas be formulated and manufactured such that the calcium and phosphorus are bioavailable and meet the calcium and phosphorus needs of infants. Calcium and phosphorus are essential for healthy bone mineralization and growth in infants. Calcium bioavailability is of particular concern because inadequate intakes of calcium impair bone mineralization and can cause rickets in severe cases (Refs. 64 and 65).

Interactions with other ingredients and manufacturing processes can reduce calcium and phosphorus bioavailability. High concentrations of calcium and phosphorus can interact to form insoluble complexes that may be unavailable (Ref. 66). Calcium can interact with free fatty acids and form soaps that are not absorbed (Ref. 66). Lactose-free formulas have been found to have lower calcium absorption than formulas containing this sugar (Refs. 67 and 68).

Some phosphorus compounds, such as the phytates found in plant protein sources, may not be readily digested and absorbed by infants (Ref. 69). Inadequate dietary phosphorus can cause a loss of calcium from the body as a result of bone resorption (i.e., loss of bone mass) (Ref. 70). Formulation or processing changes that affect other formula ingredients that influence calcium and phosphorus absorption require careful consideration of their potential effects on calcium and phosphorus bioavailability and the calcium and phosphorus status of the infant.

A dietary insufficiency of calcium and phosphorus of a magnitude that decreases bone formation may not be detected by physical measures of growth (Ref. 71). Therefore, a quality factor requirement for an infant formula to ensure that it meets the calcium and phosphorous requirements of infants, and to ensure that it contains sufficient bioavailable calcium and phosphorus for this purpose, may be needed. FDA is concerned, however, that meaningful measures for assessing the bioavailability of calcium and phosphorus may not be available.

d. *Summary.* FDA has tentatively concluded that the clinical and nutritional sciences have not reached a state where specific tests are available that would permit manufacturers to establish that they meet quality factors for each of the essential nutrients listed in § 107.100, except for protein. Therefore, except for the quality factor requirements for physical growth and protein quality discussed above and set forth in proposed § 106.96 (b) and (c), the agency has tentatively concluded that it is not useful to propose quality factor requirements for specific nutrients at this time.

Thus, to meet the nutritional needs of infants consuming formula, manufacturers must use forms or sources of essential nutrients that are bioavailable. The agency is concerned that manufacturers could unintentionally or unknowingly use forms of nutrients that have a relatively low bioavailability or ingredients or processing methods that will produce interactions that adversely affect the bioavailability of nutrients, thereby adulterating the formula because it no longer meets the nutritional needs of the infant. However, at this time, FDA is not aware of a means to systematically identify those circumstances that could adversely affect all nutrient bioavailabilities. FDA does not believe that it is ethical to unnecessarily subject infants to testing protocols when meaningful results cannot be assured. However, because of the potential seriousness of the public health impact of not meeting quality factors, FDA also believes that it is desirable to establish additional quality factors, as soon as they are warranted by evolving scientific knowledge, to ensure adequate nutrient bioavailability.

FDA, therefore, requests comment on the: (a) Need for routine testing of quality factors, in addition to measures of physical growth and protein quality; (b) criteria to be used in determining that such a need can be meaningfully implemented, and (c) if a need is established, the type of qualitative and quantitative measurements that could be used by manufacturers to demonstrate

that an infant formula meets with those quality factors. If FDA receives information demonstrating the need for additional quality factors, it will consider including them in any final rule that results from this proceeding.

5. Assurances for Quality Factors

a. *Quality factor—physical growth of infants.* Proposed § 106.97(a)(1) requires that the manufacturer conduct an adequate and well-controlled clinical study to determine whether the formula supports normal physical growth in infants when it is fed as the sole source of nutrition. The CON/AAP Task Force on Clinical Testing of Infant Formulas (Ref. 6) concluded that the capability to support physical growth is the most widely accepted and used measurement available of the nutritional adequacy of an infant formula. Gains in weight and length of young infants reflect the long-term, integrative physiological processes that can only be achieved if the infant's nutritional needs are met.

A randomized, controlled study represents the most sensitive type of study to measure the nutritional adequacy of infant formula. The use of concurrent treatment and control groups is in agreement with the CON/AAP Task Force recommendations (Ref. 6) and with the agency's recommendations for human bioavailability studies of drugs (21 CFR 320.25). Although comparisons to historical controls (e.g., population reference standards) have been used by some investigators to evaluate growth of infants consuming a particular formula product, this type of study lends itself to misleading results because population reference standards are generally for the total population of infants (regardless of birth weight, health status, socioeconomic status, or other factors that can affect growth unrelated to nutritional components). In a study to evaluate the nutritional adequacy of a formula, on the other hand, selection criteria are usually used to limit enrollment to healthy, full-term infants. Thus, differences or similarities in growth between study infants and population reference standards cannot be meaningfully interpreted. Therefore, the agency is proposing to require that adequate and well-controlled clinical studies be conducted to collect the data needed to determine whether a formula satisfies the quality factor requirements for physical growth. To assist manufacturers in understanding the general principles for adequate and well-controlled clinical studies, FDA has prepared the "Guideline for the Format and Content of the Clinical and Statistical Sections of New Drug Applications," U.S. Department of Health and Human Services, July, 1988 (Ref. 72).

FDA has tentatively concluded that it is necessary to enroll infants into a clinical study shortly after birth, and that the studies be at least 4 months in duration (see proposed § 106.97(a)(1)(i)(A)), to ensure that the study focuses on the period during which infant formula generally serves as the sole source of nutrition, and, thus, the infant is most vulnerable to a problem with a formula since the infant is not consuming other foods that could mask or compensate for a deficiency in the formula. Also, the sensitivity of growth studies for identifying nutritional problems with an infant formula is highest during early infancy. Young infants, those less than 4 to 5 months, allocate a substantially higher percentage of the intakes of energy, protein, and other nutrients for growth than do older infants. After this early period of rapid growth, the rate of physical growth slows, and the allocation of nutrient intakes for growth is lower. Thus, early infancy is the period of greatest nutritional risk and is the age associated with the most sensitive growth phase.

Because of the rapid rate of growth in infants less than 4 months of age, adverse nutritional impacts that affect growth rate can be detected within a few months (Ref. 4). Growth studies in older infants, where growth rates are of smaller magnitude and where solid foods are also consumed, are not sensitive enough to provide a meaningful evaluation of the ability of the formula to support healthy growth.

The CON/AAP Task Force (Ref. 6) also recommended that clinical studies be conducted for a period of 3 to 4 months, and that growth be examined at least during the first 8 weeks of life, because nutrient requirements per kg body weight are greatest during this period. It also pointed out that such a study will cover a period when the infant is not consuming solid foods, and the infant formula is fed as a sole source of nutrition.

Therefore, FDA has tentatively concluded that a clinical trial that lasts at least 4 months will be long enough to detect adverse effects of nutritional inadequacies on growth rate. FDA also has tentatively concluded that a clinical trial must be conducted with infants less than 1 month of age at the time of their entry into the study (see proposed § 106.97(a)(1)(i)(A)) to ensure that the formula is tested during the period of time when growth rate and nutrient requirements are proportionately greatest, and when the infant formula serves as the sole source of nutrition. These requirements are intended to ensure that the study assesses the nutritional adequacy of the formula for supporting normal physical growth in the young infant.

Under proposed § 106.97(a)(1)(i)(B), the manufacturer will be required to collect and maintain individual and group summary data on anthropometric measures of physical growth and plot the data on National Center for Health Statistics (NCHS) reference percentile body weight and body length curves, which are standard measurements of infant physical growth (Refs. 73, 74, and 75) and provide the most widely accepted assessment of infant growth (Ref. 6).

Plotting each infant's anthropometric data on NCHS reference percentile body weight and body length curves, and providing individual data on increments of weight gain, provide a means to make a quantitative assessment of the growth pattern over the 4 months duration of the study for individual infants. There is normally wide variation in body weights and lengths among healthy infants, with some being smaller than average and others average or above average. Single point measures of weight or length are difficult to interpret relative to a given infant because one does not know whether, for example, a smaller than average weight is attributable to inadequate nutrition or to a healthy and thriving infant whose body size is smaller than average.

Over time, young infants tend to individualize their track within a given percentile on population reference growth standards. An infant at the 25th percentile level for weight shortly after birth tends to stay at or near the 25th percentile for weight throughout the first few months of life. When multiple longitudinal measures of weight (or length) of an infant are plotted on a weight-for-age reference chart, a reviewer can make a quick assessment as to whether an infant's pattern of weight or length gain is similar to that expected for healthy infants of the same age, taking into account the range of normal individual variation in body weights and lengths and that infant's percentile track. Similar comparisons can be made with a given infant's weight or length incremental gain data relative to population reference standards. These data allow for identification of infants with unusually slow or rapid growth, an observation that is masked by grouped data.

Thus, plots of changes in individual infant's weight and length in conjunction with comparisons of increments per unit time of weight or length gains against population