Criteria for Determining when a Clinical Study is Needed To Establish Quality of an Infant Formula

Product Composition Perspective

A White Paper

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by

Duane A. Benton, Ph.D.
Retired (Ross Products Division, Abbott Laboratories)
Powell, Ohio

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THE DETERMINATION OF WHEN MEASURMENT OF GROWTH OF NORMAL INFANTS IS NECESSARY TO ESTABLISH QUALITY OF AN INFANT FORMULA

DUANE A. BENTON Ph.D.

The information and opinions in this paper are drawn from the author's 25 years of experience as a member of an industrial research team that developed new infant formulas and modifications of existing formulas and followed these projects to market introduction. The team addressed nutritional adequacy, safety of ingredients, packaging, processing and quality control. The management of the company and the research team believed that physical growth studies and other clinical studies were essential to the introduction of any new formula or important change in formulation.

A company has a responsibility to establish that any new or modified formula is safe and appropriate for its intended use. Experience with the proposed formulation is essential to this. Studies of other companies products is of little value since formulation, ingredients, processing and packaging differs among companies. Physical growth studies with healthy term infants are essential to this experience. Infant studies involve inconvenience and even risk for the mother and infant and should not be undertaken unless it meets an important need.

To address when a growth study is needed we should understand why a company would place such importance on such a simple but expensive study. Studies of young growing animals and infants that have identified nutrient deficiencies, imbalances, toxicity's and metabolic disorders have usually found reduced weight gain and food intake as the first sign of the problem. A growth study is believed to be a sensitive but non-specific test for disorders induced by the feeding. However, some disorders will not produce significant reductions in growth.

Growth has innumerable components and these progress in a predicable pattern in normal growth. In our experience weight gain is usually the most sensitive indicator of a deviation from normal growth. Many other non-invasive tests have been included in growth studies but are less sensitive signs of an abnormal pattern of growth. Any significant evidence that the infants growth do not follow that of the control group should lead to termination of the study.

Some propose that with the incorporation of numerous measures of physical growth in our growth study we may identify a pattern of growth more desirable than with present formulas. This may be appropriate for basic research on infant nutrition but the results will be difficult to interpret. A straight forward growth study is needed to decide whether it is safe to proceed with a new formula or a formulation change. The only answer that allows us to proceed is that the formula produces the same growth as present formulas.

The most sensitive test of abnormal growth is needed because the introduction of solid foods may resolve nutritional problems when they become a major part of the diet. Parents are not willing to delay solid food introduction very long.

It is important to start infants on their assigned feeding within the first week of life so the study includes the most rapid growth period and the period when solid food intake is minimal.

It may be appropriate to extend the study to six months of age although it increases the cost and the inconveniences to the parents and the infants. However one must be cautious not to ignore differences at three or four months because they disappeared at six months. By six months of age the rate of growth has slowed, metabolic processes have matured and solids have become an important part of the diet.

Clinical observations of a pediatrician, observations made by the nursing staff, mother's observations of the infant and nurses' resolution of their observations with those of the mothers are all essential to such a study. Where there is some problem with a formula there is usually some perception of it by the research team before there are significant differences in weight gain. Negative observations may lead to rejection of a formulation even when weight gain is not statistically different from that of the controls.

The growth study as it is used to test an infant formula for marketing is a pass/fail test. Negative results only tell you that you need a new formulation.

A manufacturer of an infant formula starts by defining what change is needed for the market. Food scientists, generally working in a pilot plant that can reproduce the processes of the commercial plant very closely, develop a stable formulation that meets all the required needs. Numerous small batches are produced to assure it will have the needed shelf-life. These are studies of changes of physical characteristics as well as nutrient levels with time. There are many chemical and physical tests that will be carried out on ingredients and final product during the development of the formula. Proper selection of tests will help us later to determine whether growth studies will be required.

One must expect that many changes will be made before a final process is accepted. Only then can the clinical study issue be addressed.

Every detail of the process must be looked at and any changes from accepted process be identified. Usually there will be one or two of the company's marketed products to compare with. In some cases there are experimental formulas that have been used in growth studies and may be appropriate for comparison.

For comparison of new and accepted formulations the following aspects must be evaluated:

1. Ingredients: The raw materials used; the manufacturers process; specifications and detailed analysis.
2. Batching: All the processes required to solublize the ingredients, homogenize and set the batch for sterilization or drying in the case of powdered formula.
3. Heat processing: Heating is essential in batching, homogenization, preheating, drying and sterilization. It is important to compare the total heat inputs that reflect the potential damage to the product.
4. Packaging: There is potential for the packaging to interact with product, leach materials into product and how the package modifies the heat input.
5. Shelf-life Changes: Losses of nutrients and physical or chemical changes during storage may indicate need for clinical evaluation of a formulation.

NEW INGREDIENTS OR CHANGES IN INGREDIENTS

Protein Source:

The infant growth study is not a sensitive evaluation of the protein quality. Infant formulas contain significant excesses of protein to support the growth of normal term infants. Only a very poor quality protein or a very poorly digested protein could be detected as inferior in a growth study. It requires a feeding of much lower protein content to estimate protein quality in infants. We must depend on other types of studies to address this important issue.

The rat PER study that is required for evaluation of infant formulas is not reliable to evaluate a totally new source of protein since the rat amino acid requirements are different from the infant amino acid requirements. On the other hand the PER can be a very sensitive test of whether a change in process or ingredients has damaged the protein in a formula. The PER like the growth study is a sensitive test indicating something is wrong with a formula but it does not tell what.

Protein sources are generally very complex mixtures. There are many ways these can interact with the nutrients so any new source of protein requires a growth study. Goat's milk has been used extensively in infant feeding but it has not been used to make a commercial infant formula. Such a formula would require a growth study because interactions of goat's milk with other ingredients might be quite different from those with bovine milk.

Bovine milk has been used extensively in formulas. A new source would not require a growth study.

However, if bovine milk is modified by making cheese, in the case of whey, or ultra-filtration is used to remove minerals or lactose, it produces many changes in the formula and must be treated as a new ingredient that requires testing.

In the case of whey, each cheese making process results in a different whey. Whey must be treated to remove minerals and control micro-organisms that are part of the cheese making process. Suppliers may have very different processes. If a formula manufacturer changes the source of demineralized whey he should either demonstrate that the processes and handling are the same as those he has had experience with or do a new growth study.

Ultra-filtration of milk to remove minerals and lactose has little potential to damage the protein or add contaminants but the process removes many nutrients that must be replaced in some form. This makes a totally new formulation that calls for study.

Soy protein isolate is the result of extensive processing of the soy bean. There can be extensive differences from one manufacturer to another in the process. The company that changes the source of soy protein isolate must demonstrate that the same process was followed or treat it as a new ingredient.

If soy protein isolate were treated by ultra-filtration to remove some non-protein component very little of essential nutrients would be removed. Nutrients would not have to be replaced in the new formulation so no growth study would be required unless the ultra-filtration added material to the isolate.

The production of a protein hydrolysate used in infant formula must be highly controlled. There is great potential for the hydrolysate to interact with nutrients and other ingredients to produced undesired responses in the infant. Small changes in the conditions of hydrolysis can produce changes in the final product. Any hydrolysate for which there is no experience is a new ingredient. Even a minor change in the conditions of hydrolysis should be the basis for detailed evaluation. The need for a growth study would be determined from the chemical and physical changes found in the product after processing and shelf-life.

Treatment of protein sources with reactive chemicals or solvents have the potential to modify the protein and to produce new substances that could interact with nutrients. It may be possible by chemical analysis and physical testing to demonstrate such reactions do not occur but it is an area where caution is required.

Fat Source:

A source of fat or oil that has never been utilized by the company for infant formula should be the justification for a growth study. Even where a fat blend has fatty acid patterns similar to human milk or accepted infant formulas this gives little assurance that the fat will be utilized in a similar manner.

The digestibility of fat blends by infants have been difficult to predict. Studies of fat digestibility in adults or experimental animals are of little value.

There have been proposals that certain polyunsaturated fatty acids in diets of infants may produce important physiological responses in infant. These fat blends are produced from materials that have never been used in infant formulas and the companies have no experience with the processing of these fat blends in a formula. The company that introduces such a fat blend into a formula has a responsibility to show not only that normal growth is maintained but that any physiological response is desirable for the infant. A growth study would be an important part of the needed research.

Fats and oils contain many substances that have potential for adverse reactions. We do not know what all of these may be. Chemical or physical modification or fractionation of a fat source must be assumed to have produced a new ingredient since contaminants may have been concentrated or new substances been produced.

In the Infant Formula Act digestion and utilization of nutrients has been specified as a quality factor in infant formulas. Milk fat has been used in infant feeding for many years. Nutrient balance studies with new born infants have demonstrated it to be poorly digested and absorbed. Growth studies with milk fat containing formulas do not show poor growth but will show an increase in formula intake if it were measured.

If companies must show the digestibility of the fat blends in their formulas then nutrient balance studies in new born infants will be needed. No animal model has been found to be a good predictor of the digestion and absorption of fat blends in new born infants. The conditions to carry out such studies may be very controversial.

The digestion of a fat can't be predicted from the fatty acid pattern alone but is a function of the specific triglycerides in the blend. A company that claims a fat blend is like human milk or is a source of important long chain polyunsaturated fatty acids should show that the fat is well digested and absorbed.

All rearrangements or fractionations of previously used fats would seem to produce new ingredients that need testing. It may be possible to show that some triglyceride fraction is so pure and evidence for utilization so clear that no clinical study would be needed. This would require chemical and animal studies.

Carbohydrate Sources:

Lactose, sucrose and corn syrup solids have been used extensively in infant formula and most companies have enough experience with each of these to not be viewed as a new ingredient. Changes in the proportion of these carbohydrates have never modified infant's growth responses to experimental infant formulas. This is based on studies using commonly accepted processing methods.

There are processes for making soluble oligosaccharides from starch that result in quite different products from the usual corn syrup solids. Before such a product is used to replace corn syrup solids in a formula its chemistry and digestion should be looked at in detail. It might have to be treated as a new ingredient if it were found to be very different from the usual corn syrup solids.

Reducing sugars tend to interact with many other ingredients in a formula. A carbohydrate mixture that has significantly greater reducing activity than previously used carbohydrate would justify a growth study. Formulas which use protein hydrolyzates, free amino acids or amino acid supplements would be of special concern.

Other carbohydrates proposed for infant feeding such as lactulose are not intended to be a primary energy source but are proposed to stimulate the bacterial flora These are generally poorly digested and absorbed by the infant. They will result in gas production and may cause some intestinal disorder if the level used is too great. Some controlled study in infants would seem necessary to justify any use in formula.

The author's company had extensive clinical experience with milk based formulas in which added lactose was replaced with corn syrup solids with no effect on growth of infants. Other companies may have similar results. No problems have ever been reported.

Mineral Sources:

There should be extensive experience in the food industry and with animal feeding with any mineral source used in an infant formula. The Infant Formula Act controls effectively the levels of essential mineral element in formulas. Chemical analysis should show that no toxic materials are present.

With the minerals sodium, potassium, chloride and magnesium the commonly available salts seem to be easily absorbed. Calcium and phosphorus can be converted to forms that have reduced availability in animals. Only a severe reduction in the availability of calcium and phosphorus in a formula could be

detected in a physical growth study. These elements are usually added at levels well above those required by infants.

It is not likely that deficiencies of iron, copper, manganese, molybdenum or iodine would be detected by the usual physical growth study because of the reserves that infants usually have at birth. Other types of research are needed to prove that these trace elements in infant formula are available.

The balance of various minerals in a formula must be of concern. For example dietary sodium, potassium, chloride as well as calcium and phosphorus have effects on the acid-base balance of the infant. It would be possible to produce an acid-base problem within the ranges of these elements allowed in the Infant Formula Act. Radical changes in the ratios of these elements would require a growth study.

Small changes in a mineral mixture of a formula probably does not justify a growth study. A major change for which there is no similar experience would justify study. It is important to evaluate whether a growth study is the proper way to address the issue.

Vitamin Sources:

The vitamin mixtures of water-soluble and fat-soluble vitamins that are presently used by the industry have proved to be highly reliable. There are losses of some vitamins during processing. This is required to be tested regularly by the company in each formula and each container type and processing system. Quality control tests demonstrate the mix has been added and at the appropriate level. There is no reason to change how this is being done.

If for some reason a company needed to change the form of some vitamin in a formula it would do all the required studies of the new pre-mix. This would show that all the vitamins in the premix were stable during the storage life of the premix and it would show what losses there were during processing with the new premix. There would seem to be little need for a growth study if the new form of the vitamin was well established as active for the infant and the analysis of the vitamin in the product showed no problem..

Ascorbic acid must be considered differently than other vitamins. Ascorbate is unstable in all infant formulas during batching and heat processing. It is always added as the last ingredient and levels are monitored throughout processing. It is only stable in liquid formula when all the oxygen has been destroyed, primarily by the oxidation of ascorbate. If a container is slightly permeable to oxygen it will be necessary to add more ascorbate to assure adequate levels throughout self-life. If a batch of formula has to be held for a prolong period before processing and packaging it will be necessary to add more ascorbate before the batch is finished.

Infants and adults have been demonstrated to tolerate very high levels of ascorbate. It is less clear what effect the breakdown products of ascorbate might have. The author's company conducted some growth studies with formulas that had experienced extensive ascorbate loss. These studies were used to set the maximum amounts that the plants were allowed to add to any batch. If very high levels are going to be required with certain formulas it may be necessary to do growth studies with the maximum fortification levels.

Food Additives

The FDA allows the use of food additives in foods if it has accepted it as generally recognized as safe (GRAS) or if a food additive petition has been accepted by the FDA. Rarely have food additives for infant formula received the detailed evaluations that would seem appropriate. Carrageenan is an exception to that.

The new born infant will receive a much higher dose of a food additive per kg. body weight than will be the case with any other food. This is true because infant formula is the sole source of food for the infant and because the infant has a much higher caloric requirement per kg. body than older individuals.

Experience with a modified starch which the FDA recognized as GRAS may be useful to the reader. A food scientist with the author's company demonstrated that it was much more effective in stabilizing hydrolysate formulas than other additives and patented the use.

It was required at rather high levels to be effective and the starch part of the additive was a significant sources of calories. Studies with rats suggested it was well tolerated but levels fed were limited because the additive became the major caloric source in the rat diet.

Additives are generally fed at 100 times the typical intake on a per kg. body weight basis in safety studies. In this case the infants would typically receive one quarter the maximum dose from the animal studies. The additive had never been studied in newborn animals.

The company under took studies in puppies and the growth rate seemed poor. The company also studied how the additive was metabolized in the rat and found large amounts of previous unknown organic acids were excreted in the urine.

At this time a researcher studying infant's urines detected similar acids in the urines of infants fed a competitor's hydrolysate formula. This additive was being used in commercial infant formula without any controlled studies in infants and certainly no knowledge of the organic acids they would excrete.

Although our company did further animal studies and a few infants received experimental formula the company and the investigators decided to discontinue the study. The author's company never used the additive in commercial formulas because we didn't believe that it could be shown to be appropriate.

If a company plans to add any additive for technical or physiological effects and it has no clinical experience with the ingredient they should conduct at least a growth study at the level required for the projected effect. But before that is done there must be complete knowledge of the additive's metabolism and safety studies in newborn or at least young growing animals are needed.

Additives may have impurities, potential for interaction with nutrients and may break down to products the infant is sensitive to. Use in the general food supply or use as a nutritional supplement is not likely to identify such a problem.

Batching and Heat Processing

The food scientist in developing a new formulation has the objectives of the best possible appearance, taste, smell and stability. All the essential nutrients must remain intact as shown by chemical analysis. These are severe challenges with the complex materials that the nutritionists want to add to the formulas.

Adverse reactions among ingredients must be avoided by controlling the order ingredients are added, temperature, time, pH and many other factors during the process. Likewise avoidance of interaction among ingredients is most likely to maintain the nutritional quality of the product.

When a proposed change no matter how small and insignificant has caused physical and chemical problems, it raises suspicion that a nutritional problem may be encountered. Physical changes in the formula indicate that a growth study may be needed.

To prepare a batch of formula to survive heat processing it is usually necessary to increase the pH and to increase citrate levels to chelate calcium and magnesium ions. These adjustments serve to stabilize the emulsion. If the pH of the formula is too high there will be severe browning which indicates reactions have occurred between the carbohydrates and the protein. The color, smell and odor of severely browned formula would be unacceptable to a parent and might produce nutritional problems for the infant.

Changes in the batching process could produce interactions among ingredients that compromise the nutritional quality of the formula and still produce a physically acceptable product. Each proposed batching change should be reviewed for potential interactions of ingredients and might require a growth study.

Sterilization

High temperature treatment of liquid formulas is needed to kill heat resistant spores. This treatment must be held to a very short time or the physical and nutritional quality of the product will be lost. The heat treatment is either in the container or in a flow-through heating system. Some formulas require both.

Most formulas would not tolerate significantly greater heat input. However there are times that the sterilization process has to be modified for a change such as a new container.

If a change in sterilization results in a significantly greater heat input to the product a growth study is needed.

There are numerous chemical reactions that can be monitored during processing to determine if a change in the heat process results in damage to the formula. These include destruction of vitamins, browning and the production of various aldehydes and ketones.

Comparison of the F sub O values for two processes is not adequate since many nutrient interactions proceed at temperatures well below those needed to kill bacterial spores. Slowing the preheating and cooling processes in sterilization can have very adverse effects on the formula. Expert analysis of the process is necessary to conclude that a growth study is or is not needed.

Packaging

The packaging used for infant formula should not be viewed as inert and unimportant. There are materials that leach from properly coated steel cans. Although the levels of such materials pose no direct risk to the infants they might serve as catalysts for nutrient interactions that occur during sterilization and shelf-life. The surface of a can or bottle may serve as a catalyst for some reactions also.

Evidence of damage to the formula or an unusual residue in the product following a change in the packaging are justification for a growth study. Experience from the general food industry with a new container gives little assurance that it is appropriate for infant formula.

Plastic containers are now used for infant formulas. These are complex structures because a layer in the plastic must block the passage of oxygen into the formula.

Materials may leach from such a structure. Oxygen will pass through to some degree. Changes in formula during shelf-life may be quite different between a steel can and a plastic can.

Heat transfer is much slower through plastic walls than through steel walls so the preheating and cooling stages are slower in the plastic. Since plastic containers will not tolerate the high temperatures used in steel or glass containers the sterilization stage must be at lower temperature and therefore longer time. These processes may increase damage to the product.

Infant formulas are being aseptically processed and filled into sterilized plastic containers. This means that the formula is sterilized in a flow-through system and then packaged in a chemically sterilized plastic container. This results in much less heat damage to a formula. The manufacturer must assure that any residue in the package can not damage the product.

Are ingredients and processes that are safe in one formula safe in all possible formulations? There is no simple answer to that question. Every detail of a specific question must be studied before an answer is given.

Change is very common in the infant formula industry as it is in most industries. Changes have many advantages to the user of the product and some are produced by changes in regulations.

There are a number of new ingredients that are proposed to have significant nutritional benefits for infants. If one of these were added to all the different infant formulas of the company the author worked for there would have been more than 40 formulation changes. Each of the basic formulas is produced in different forms (ready to feed, concentrated liquid and powder) and different containers (steel cans, glass bottles, plastic cans and plastic bottles).

For each of these formulation changes the company would study physical stability and nutrient stability for the shelf-like of the product because even minor formula changes can alter these. If a physical growth study were conducted for each formulation change it is hard to believe that the company would be able to find enough qualified research teams to conduct the studies. Certainly the number of infants and parents that would be exposed to the inconveniences of a study would be hard to justify.

It would be impossible to justify a growth study for each formulation so decisions must be made on how a few growth studies will establish the safety of all the changes. These are difficult decisions.

It has been proposed that if a new ingredient is found to be safe in one formula then it should be safe in all formulas. This assumes that there is no importance to interaction of ingredients, processing and the many other differences between formulas that are discussed above.

This must be rejected. The industry would never accept that a new ingredient that produced no change in physical stability of one formula could be added to all other formulas without physical stability studies. Why would nutritional quality not have a similar standard?

There are proposals that any ingredient that has been used in any company's formula could be used by any other company without growth studies. This would assume that none of the aspects of processing, sterilization and packaging that are unique to a company have importance in nutritional quality. This must be rejected.

If these proposals were accepted it would be possible for a company with experience in food processing but no experience with infant formula to make a formula from a variety of ingredients used by other companies in different types of formulas and put it on the market without any growth studies.

There must be a way to evaluate from a companies experience what growth studies are necessary and which are not, out of all of the formulations that result from the addition of a new ingredient to the companies products. It must not reject as unimportant any of the potential interactions of ingredients and processes that are listed above. This requires a detailed knowledge of all the manufacturing process in each of a companies products.

The companies staff are the only people that know all details needed to prepare a proposal concerning the need of growth studies caused by a formula change. Knowledgeable individuals outside the company would be able to evaluate the thoroughness and the scientific soundness of such a proposed plan.

Criterion:

The author is aware that criterion are needed to establish if a growth study is needed. Below are a series of steps the author has followed when faced with these decisions. It is assumed that any formula is in some way a modification of some formula that has been adequately studied. If this is not the case than it is without question a new infant formula and a growth study is required.

Evaluate the chemistry of all the new materials added. This must include both the substances added for a functional propose and materials that are carried along. It must identify potential reactions with other

ingredients and the products of any such reaction. Chemical and physical methods of analysis are used to identify whether such reactions have occurred.

Evaluate the infant's potential metabolism of the new added materials and any reaction products. If such information is not available in the literature it may require research even before a physical growth study can be considered.

Evaluate whether the new formulation requires new batching procedures, heat processing or packaging. Chemical and physical methods of analysis are used to look for interactions between ingredients such as reaction between carbohydrate and protein, lose of vitamins or changes in chemical state of minerals.

Evaluate all the experience the company has with well studied infant formula to determine if any of the historic experience can appropriately be applied to the new formulation.

Identify from the literature any physiological effects that could possibly be elicited by the new formula that would not be expected from commonly accepted formulas. Where any such effect can be projected a physical growth study is needed.

If these evaluations show that the new formulation has no evidence for unexpected interactions among ingredients and nutrients, unfamiliar metabolic products or physiological activities, then it may be appropriate that a growth study is not required. One should use caution in drawing this conclusion.