and then provide some additional useful information, examples, and matrix questions.

Some findings from pre-term studies can be readily generalized to term studies, term infants. This deals specifically with issues -- next slide -- of the fact that we are, as Dr. Caplan stated, on a continuum pre-term to term.

This is a continuum of maturity. So study one, an example in extremely premature infants may not be completely generalizable to term infants. However, an example of study two started in late pre-term life and continuing well into term infancy could have a great deal of importance and be able to be generalized to the term population.

Next slide. Just very quickly, two examples. Fat absorption. Again, Dr. Caplan actually mentioned this. Similar in pre-term and term and increasing at the same rates, the study that was published earlier this year.

Next slide. The LSRO, Life Science Research Organization, under contract to the FDA, evaluated nutrient requirements of pre-term infant

formulas and stated in the conclusion of protein digestion considerations that the data concerning protein digestion of infants 32 weeks and greater of gestational age are equal to term, full-term infants. The quote is there in front of you. Indicating the similarity of these healthy, relatively late gestation pre-term infants.

The next slide will then let us move quickly on to some findings in pre-term infants that are especially relevant. This deals with the susceptibility of growth perturbations and adverse events coming from pre-term to term studies.

The next slide indicates just our compilation of data, looking at grams per kilo per day of body weight gain. You can see pre-term infants are gaining weight much more rapidly than term infants, and the term neonate actually gains weight much more rapidly than later during the first year of life.

It's important to realize that the FDA has already accepted the generalization concept, moving from a term neonate during the first few months of

life, generalizing data from that type of study to later during the first year of life.

Next slide. This gives you an example of one study that we have conducted, effects of growth and safety on long chain polyunsaturated fatty acids in pre-term infants, and I note that one of the members of the advisory board, Dr. Heubi, was a coauthor of this study, where we evaluated growth and adverse events from approximately 32 weeks gestational age to 48 weeks, and also looked at serologic markers and safety.

I'll give you one piece of data -- next slide -- which is weight gain in the formula plus LCP control formula and human milk fed group that was fortified with the human milk fortifier. We see weight gain during the entire course of this study and we actually then continued evaluation of post-study feedings into later during the first year of life.

We see no differences in weight gain between the two formula groups, allowing us to generalize the concept that, in fact, these

additions are safe, and we would generalize that notion not only from this study, but to term infants.

And the next slide will let us look at -- I'll come back to matrix in a minute. But what other supporting information might be useful? Certainly, GRAS data, systematic reviews, comparing pre-term and term data, nutrients found in human milk and something that we would know about their variability, and, also, worldwide history of use in term and pre-term formulas.

Next slide. Addressing formula matrix concerns, my last point, composition of formula limits the potential for nutrient-nutrient interaction. Term formulas are regulated by -- the compositions are regulated by specific regulations. You've already heard something about that.

Pre-term formula by authoritative recommendations. We know a great deal about then the range of expected nutrients in term and pre-term formula that will allow us to address matrix concerns.

You've heard from the FDA this morning considerations of bio availability. Let me give you two examples of what we would know about bio availability.

Next slide. Now, specifically, in pre-term, LCP dose responses, we've looked at control formula, three doses of LCPs, and compared that to human milk, to allow us to understand matrix interactions.

We have looked specifically -- this is plasma arachidonic levels we're looking at. We've looked at the entire lipid profile in the circulation of the infant to understand any differences between the matrices.

Next slide. We've actually conducted a very similar study in term infants, control formula, three doses of specific LCPs, and, again, compared to human milk.

So yes, in fact, when we generalize data from pre-term safety studies, we feel that there is quite often the use for additional supportive information, such as these bio availability studies

and all these studies conducted by GCP.

Next slide. Then the last two points here are experience of the manufacturer. We have a great deal of manufacturing experience as to the other companies in the U.S. with regards to food science, nutrient-nutrient interactions during the manufacturing process and stability throughout the shelf life of the product.

In addition, clinical assessment across multiple matrices and manufacturers, published data coming from a variety of matrices indicating potential interactions are also quite useful to address matrix concerns.

Let me summarize on the next slide. In the conclusions, findings from pre-term infant studies can be generalized to term infants based on these components; the quality of the studies under consideration, the relative maturity of the pre-term group, the amount of supportive data in addition to the clinical studies available, commercial experience across a variety of manufacturers, and understanding the effects of the

formula matrix.

Thank you for your attention.

DR. GARZA: Thank you very much. Are there any points of clarity? Dr. Dwyer?

DR. DWYER: Does findings mean lack of adverse events or does it mean benefits?

DR. LIEN: No. We're talking here about safety issues. We're not talking about benefits. We're talking about the potential for adverse events or concerns related to growth, healthy growth.

If there's 15 seconds left in my time, I would like to --

DR. GARZA: Go ahead.

DR. LIEN: -- direct your attention. I picked up the letter from Dr. William Heird on the back table. Dr. Heird is chairman of pediatrics at Baylor and also --

DR. GARZA: Dr. Feigin might disagree with you on that one.

DR. LIEN: I'm sorry. What's that?

DR. GARZA: I said Dr. Feigin might

disagree with you on that.

DR. LIEN: Dr. Heird is associated with USDA Children's Nutrition Research Center and certainly does do work at Children's, Texas Children's.

I see in Dr. Heird's letter a comment that I might just draw your attention to, on the second page, and he states, "I can think of no physiologic system that is not more vulnerable to safety issues in the pre-term than in the term infant."

So he's saying the pre-term infants are more vulnerable. We realize that. Thus, if this is the case, I feel comfortable concluding that a quality factor evaluated in pre-term infants as a component of pre-term formula and found to be safe is more likely -- is likely to be equal, if not more so, as a component of term formulas, intended for term infants.

DR. GARZA: Thank you. Dr. Pamela Anderson, also on the generalizability of clinical studies to term infant formulas.

DR. P. ANDERSON: Good morning. I am here

representing Ross Products Division of Abbott Laboratories. I am the Director of Regulatory Affairs.

These comments I am presenting today are on behalf of our medical staff, Dr. William McLean, and Dr. Russell Merritt.

In the interest of time, I will move forward a little bit quickly through my talk and will not present all of it today, but you do have it in the paper there before you.

What I want to do is to be able to expand on and extend the comments of Mr. Gelardi and, in doing so, give you a Ross perspective on the issues.

The committee has been asked to consider whether clinical data derived from clinical studies with pre-term infants can be used to support IFA notifications for formulas destined to be fed to full-term infants. Related to that question is one of whether data from the clinical testing of one formula can be used to support the modification or introduction of another formula.

Our view is that one cannot give a definitive yes or no to these questions. Rather, a decision analysis approach is needed.

The analysis needed and the conclusion reached may be different for different nutrients, ingredients, or compounds. Keep in mind that while an infant formula must meet the nutrient needs of the infant, these nutrients are provided by ingredients which provide more than one nutrient; for example, milk protein, which provides not only the protein, but provides calcium and sodium, et cetera.

In addition, the ingredients used may or may not provide the nutrient of interest in the same biochemical form as found in human milk. For the purposes of discussion and to be able to lay them before you, we have enumerated how the ingredients and nutrients could be broken down into general categories. First, there is the standard nutrients, the IFA required nutrients.

The second are other nutrients, those not required by the Act, which would be something like

taurine, carnitine, or the long chain PUFA, as we have talked about today, ARA and DHA.

The third are other non-nutritive compounds that could be found in breast milk, such as oligosaccharides.

A fourth group could be novel components, which we still have not defined or have thought of at the present time, as we are continually an evolving group in science.

Lastly, it would be food additives.

So in thinking about these modifications to formula in each of these categories and the clinical studies carried out to support them, one needs to consider whether the data are directed at assessing the safety or suitability, bio availability, the growth, or the efficacy.

Indeed, the safety and efficacy may have very different meanings for different classes of compounds and depending on the reason for their proposed addition to the formula. Safety and efficacy of standard nutrients in the IFA table, for example, imply fully meeting the infants'

nutrient needs and safety also implies an absence of the undesirable side effects.

With that as background, I would like to look at these four areas of provide examples of conditions in which pre-term data may not only be informative, but directly transferrable to term infant formulas, and also provide examples of conditions in which it clearly could be unwise to rely only on pre-term data alone, and I have split those out in the paper that I have presented to you.

In the first area of safety, we want to provide two examples, simple examples. In our experience, for instance, a GRAS food processing aid, such as an emulsifier, that has been found suitable for use in pre-term formulas by way of a clinical tolerance in growth study in pre-term infants would fully be expected to be suitable for term infants and should, therefore, not require clinical study.

On the other hand, a formula with a high content of phosphorous and possibly also high

contents of Vitamin A and D could be shown to be safe in a clinical study of growing premature infants, but could lead to medical complications in term infants.

If the high mineral and fat soluble vitamin formulation were thought to be suitable for full-term infants, the clinical study documenting the safety would have to be carried out.

Under bio availability, the mechanisms for the digestion and absorption of protein are well defined and the same in both pre-term and full-term infants. A nitrogen balance study showing good nitrogen absorption of bio availability of a protein source in premature infants whose digestion and absorption may be somewhat compromised would be applicable to full-term infants.

We and others and have sponsored and carried out nitrogen balance studies over a number of years and we know of no exceptions to this rule.

On the other hand, the mechanism of absorption for some nutrients differs with age, as has already been pointed out. A good example of

this is the calcium absorption, which is primarily dependent on calcium content in the formula for the premature infant and more dependent on Vitamin D in the full-term infant.

In these situations, results from a pre-term study may be of interest, but would not be fully applicable to a term infant formula.

For growth, we know a considerable amount about the protein requirements of both pre-term and full-term infants. A protein source that supported normal physical growth in premature infants would be expected to support normal growth in full-term infants when used at appropriate levels in term formulas. Consequently, no additional clinical study would be required.

On the other hand, a formula high in phosphorous, as said before, could be desirable for normal growth in prematures, but might lead to neonatal hypocalcemia and seizures in full-term infants.

For efficacy, there has been some full-term and pre-term infants that may have allergies

to whole protein. A clinical study that looked at a specific protein hydrolysate and found it to be hypoallergenic in pre-term infants with documented milk protein sensitivity would also be expected to be applicable to term infants.

The reverse also is true. A rigorous challenge study of a hydrolyzed protein in full term or older children with documented milk protein sensitivity would be directly applicable to use in pre-term.

In the area of the long chain polyunsaturated fatty acids, this provides an example in which ingredient efficacy in one group cannot be directly transferred to the other. In our clinical study program of ARA and DHA, we found a benefit of the addition of these ingredients in the pre-term infant. It was greater in the smaller infants, which makes biological sense, since these infants are the group most greatly deprived of transplacental transfer of ARA and DHA.

Our full-term data from two other large randomized trials showed no benefit for the

addition and, thus, in the area of efficacy, the data would have to be developed in products destined for each group of infants.

The committee has also been asked to consider whether data from one formula might be applicable to another formula. In many instances, the information learned in the clinical study in one formula is easily transferred to another formula. For example, in developing the current fat blend used in most of our products, fat balance and growth were assured in one product and the blend was then used in a number of products.

In our judgment, it would not make sense, for example, to do a separate study on the same fat blend of Similac and Similac Lactose-Free or in Similac and Isomil.

MS. HAYDEN: You've got 30 seconds.

DR. P. ANDERSON: Thank you. Our long experience has shown that fat blends behave similarly in all of these products, and there are other areas in which the product matrices of the processing parameters are sufficiently different

that data derived in one formula may not predict the effects in another.

Our practice is to go through a decision tree analysis and in making such analysis, we use our knowledge and experience in ingredient sourcing, product development, food processing, sterilization, and in addition to our understanding of pediatric nutrition.

Having said that, we believe it's both unreasonable and unethical to conduct studies simply to check a regulatory box if no useful information will be gained and the current individualized decision tree approach is the best way to meet the industry's and the public's mutual goals.

Thank you.

DR. GARZA: Thank you. If you will be staying until the end, perhaps we'll have some questions after that.

DR. P. ANDERSON: Fine. Thank you.

DR. GARZA: Dr. Hansen, on the role of clinical trials in the development of infant

formulas.

DR. HANSEN: While the slide is coming up, I am Dr. James Hansen, Medical Director for North America for Meade Johnson Company. I have been involved in infant nutrition related research for a number of years, in fact, my entire career, and have, as Meade Johnson has as a company for its entire existence, been involved in infant nutrition, and this spans nearly a century of research and development.

Some of the highlights or hallmarks of that research and development have included the introduction of new infant formulas for which research was done before introduction, spanning from 1929 to 2002, a number of seminal events, including the soy and subsequently soy protein isolates, the extensively hydrolyzed protein formulas, and an offshoot from them are the metabolic products, as well as premature infant nutrition, and, most recently, the first infant formula with the AHA, arachidonic acid, in the United States.

The objectives, our objectives in doing research is to work with FDA and outside experts to maintain appropriate standards for the development of infant formula. We also ant to be sure that we cooperate with the FDA in making sure that there is access to necessary expertise to work collaboratively with industry to design appropriate clinical trials of new infant formulas and wish also to not only keep the GCPs or good clinical practices, which is a given, but also to maintain other high standards, scientific standards to ensure the protection of these vulnerable populations.

Now, infant formula development has actually been addressed somewhat in the code, the U.S. Code of Regulations, and they mention that human milk -- that formulas are a human milk substitute by reason of the simulation of human milk, establishing the goal for term infants of producing a product that is close to human milk, both qualitatively in terms of the nutritional components, and also with regard to the levels and

ratios, which, however, because of differences in bio availability and so forth that have been discussed, may have to differ from those levels in human milk itself.

However, the goal for pre-term infants is quite different. It is not to mimic the performance of human milk in the pre-term infant, because of the unique requirements the pre-term infant has to meet their rapid growth needs that would be similar to those that are in utero.

So the goal is quite different, not mimicking the performance of human milk, but rather to meet their unique growth needs of the pre-term infant.

Now, there are several reasons to conduct clinical trials in infants, in infant feedings. One is if there is a new ingredient or a new source, and such would need to be thoroughly evaluated to make sure that that source is indeed safe and that for any efficacy that's expected specifically beyond growth, that that would be there, as well.

However, the appropriate design of these various clinical studies can't be just boilerplated into a single protocol. It needs to -- it requires the input of experts that extend beyond any one group or institution, including Meade Johnson's research department or even the FDA, but we rely on the academic community at large to obtain the expertise in order to make sure that the studies are designed appropriately.

The role of growth studies has been articulated quite well here already today and the pivotal role it plays in establishing the safety of infant formulas.

Now, concerning the generalization of results from clinical studies, typically, we would see that a major reformulation or the addition of a new ingredient would most often require clinical studies. However, minor changes to a formula may be supported by well accepted scientific rationale and that may be possible without actually engaging in a separate clinical trial, such as the adjustment of a trace element or a mineral level or

a vitamin level that might be based on recommendations of acknowledged expert groups or bodies.

Now, when adding a new ingredient to formulas, the difference in the formula matrices must be considered because the different formulas are different and the matrices are, therefore, different, and that should be taken into account when considering whether or not it's generalizable between formula matrices.

The potential -- now, looking at the generalization from pre-term to term infants, there are important differences that have already been discussed between the term and the pre-term infants, both in formulas that are available for them and in their physiological needs.

Data obtained from pre-term infants may not provide a sufficient level of information to assess suitability for term infants. A couple of examples have been given by the previous speaker about how, for example, Vitamin D is required in fairly high levels and Vitamin A and so forth in

pre-term formulas. And if you give pre-term formulas to term infants, they can approach levels that have been -- would approach the toxicity intake for those vitamins, if given freely out of the marketplace.

So the pre-term formulas cannot always be -- information cannot always be generalized to the term infant.

In certain situations, however, pre-term infants may serve as a model for nutrient availability in term infants, as has already been pointed out by others.

The reason we -- in looking at generalization from different formula matrices, I have already mentioned that they are not identical and even those with the same intended use may be considerably different. For example, the fat blend and the other fatty acids that are present in one term formula may not be the same as the other.

So that the information regarding a modification of the fat or the addition of something like even the LC PUFA may have a

different interaction as far as the substrates of essential fatty acids that might be provided in the different matrices, the different formulas.

Differences in proteins and fat blends may limit this ability, as I have just indicated, and the ratios and levels may also be important in this process.

MS. HAYDEN: You've got 30 seconds.

DR. HANSEN: Okay. I'll just go to the last two slides then here. The chemical form of the ingredients, important. And in summary, a major reformulation will typically require clinical studies. Generalization of clinical results to support minor formula changes requires that the source of nutrients of the formula matrix are adequately considered.

Extrapolation of results from pre-term studies to term infants may be appropriate in a limited set of circumstances.

Issues to be considered. The FDA should continue to work with experts from academia and industry to determine the appropriate design of

clinical studies specific to the particular modification of the formula being considered and FDA requirements for clinical data must apply equally to all manufacturers.

In other words, the innovators should not necessarily be held to a different standard than those who would follow.

Thank you very much.

DR. GARZA: Thank you, Dr. Hansen. I would hope that all six of our people that have presented to us are still available. So that if you have questions for either Dr. Hansen or any of the other five, let's get them on the table.

Virginia, you had a question, I think, of the previous speaker.

DR. STALLINGS: Really, I've clarified it over the course of the speak. So I don't want to -- it's not Dr. Anderson's to answer by herself, but I think there are really two issues, as I've been listening to this.

Being a pediatrician has actually been responsible for delivering nutrition support in an

intensive care unit, a neonatal intensive care unit. The two things that I don't think any of us have been discussing yet is term infants are healthy babies. They are healthy children.

If we're lucky, during those first four months, the worst thing that's going to happen is they're going to have a couple of ear infections and maybe an episode of diarrhea.

Premature infants are entirely different. If you're in a nursery, you appreciate that we are actually working in an environment of illness, not just prematurity, that they are subjected to what we do to them to help them survive the stresses of being there, often the infections.

It is such a different environment. So that is one issue. Then the second issue, just to get them both on the table. The other, in a term infant, we always assume, and most of the time we're right, that they have undergone normal gestation and growth and that the mother was in relatively good health and it resulted in a term infant born with normal nutritional stores and with

the normal nutritional status.

In the premature infant, the other thing that I think we have to consider is I think that they are often born with different nutritional status. So their growth, where they are when they're born, and, also, the issues of maternal health. They may be born with different nutrient stores and then they all come with different reasons for having been born early. So the clinical scenario that results in premature birth.

So whereas I agree with much of the physiology that is being described, what I find that is absent is the other part of being a premature infant and what that might be doing both to metabolism and thus a lot of these nutrient issues, and, also, just the environment that they're in that they are trying to grow.

So I'd be happy to have any comments from any of the speakers on this issue of the healthiness of term babies and the unhealthiness and the variations of nutritional status when premies are born.

DR. GARZA: Dr. Hansen, would you like to address that or refer it to one of the other speakers?

DR. HANSEN: I concur with Dr. Stallings' comments. We are dealing with a different population, not only physiologically, but in the milieu of sick -- illness, as well, and those all do create a unique circumstance for the premature infant and can impact dramatically on nutrition.

I think one of the examples of that is the Vitamin A need of the pre-term infant with regard to pulmonary disease and the connection that has been shown. At least some studies have suggested that higher Vitamin A may help with the -- part of the reason for high Vitamin A levels in premature infant formulas, they help with the pulmonary disease.

That's just one example. Any other comments that anyone else has?

DR. CARLSON: I would just say that --

DR. GARZA: You have to get a mic. Go ahead, Dr. Carlson.

DR. CARLSON: I think, Dr. Stallings, I agree also with you that there are a lot of other issues, but I see that all of the ones you raise really relate to the vulnerability of the pre-term infant and I think in the interest of time, we were all trying to focus on one type of vulnerability, which is just the physiologic immaturity of these infants.

But clearly Dr. Anderson's comments about a decision tree approach I completely agree with. I think that it totally depends on the nutrient and you have to take the whole body of research into account.

DR. STALLINGS: What is the youngest, when you're thinking of your premature infant formulas, what is the youngest gestational age that you imagine those are being fed to when they are designed and tested?

DR. HANSEN: In the studies that we have done of premature infant formulas, we have been feeding them for babies down as -- we've not put a lower limit. What we try and do is stratify the

studies, randomization, stratify them so that they're all groups that the premature infants are represented in all study groups.

So that there will be some babies in there that, in order to make it generalizable to the pre-term infant, we felt it important to look at all groups. So we haven't -- originally, we used to say a 1,000 grams or more, but we don't do that anymore because there are so many babies less than a 1,000 grams that need pre-term formula that we include them in our studies as well now.

DR. GARZA: That's full nutritional support?

DR. HANSEN: Pardon?

DR. GARZA: That's in full nutritional support.

DR. HANSEN: Yes. Usually, our studies ,we wait until they are receiving full nutritional support enterally and so that's usually the commencement of our premature clinical trials, after they're on full -- almost full -- at least a 100 ml per kilo per day of formula, enteral

feeding.

DR. MOYER-MILEUR: May I comment?

DR. GARZA: I think Dr. Lien wants to make a comment, then we'll come back. On the same question that Dr. Stallings raised?

DR. LIEN: We would agree that there is -- the pre-term infants are a population in jeopardy from a health perspective. I think one consideration that has to be given is the examples that I provided that a study in extremely low birth weight infants may have a great deal of difficulty in terms of generalization to a term population.

You're looking at a healthy population of relatively late gestation pre-term infants, perhaps a mean birth weight of 1,500 grams, where you see few feeding problems and a very rapid approach to full enteral feeds, normal maturational process.

We feel that this type of population has a great deal of generalizability. So I think you could be looking at actually a continuum in the pre-term population of disease and generalizability.

I see Dr. Caplan here, too. I might just ask him to comment on that, if that's what you're up here for.

DR. CAPLAN: I don't think I have much to add, in addition to the fact that despite the fact that studies of the premature formulas were done on the bigger, quote-unquote, babies, we do have to use them in 400 and 500 grammers and we have to be careful there.

But I think that the question for today is really the flip-side as to how we can generalize the premature study to the term baby and I think that's a very different issue.

DR. STALLINGS: A very brief follow-up. What do you think the youngest gestational age baby is that premature infant formulas are given to? Not at the full amount, but just so the committee understands how young or how small they might begin to be offered enteral feeding.

DR. CAPLAN: Last week I started a 400 grammar, who was 24 weeks, on enteral feedings with one of the premature formulas, because the mother

was nowhere to be found to give breast milk. So that's what we had to do.

DR. GARZA: Thank you. Dr. Moyer?

DR. MOYER-MILEUR: I think we need to consider the fact that when these clinical studies are done, feeding studies in pre-term babies, in order to meet the study criteria, which it would be, for the most part, a 100 ml per kilo per day, that most of your babies less than 27 weeks gestation or less than 1,000 grams will not meet study criteria.

So I think that they are predominantly under-studied and I don't think the nutrition needs of those babies are appreciated.

The other worry that I have is the thought that studies of older gestation pre-term babies, say 31 to 34 weeks, are similar to those of term babies and while that might be true, conversely, I would hate to think practice would change, accepting that term baby studies are applicable to that specific population. I think they still have special needs that have to be recognized.

DR. THUREEN: In addition to Dr. Moyer-Mileur's comments, I would like to just say that the population of infants less than a 1,000 grams available for study in this country is actually quite small.

Out of the total population of, what, four million births a year, only about 4,000 to 4,500 are less than a 1,000 grams. So studying that population is not really feasible and most of those infants, probably 26 weeks to 27 weeks gestation, most of them would be on full enteral feedings to -- at the youngest to be studied.

So studying that group in detail is not going to be feasible.

DR. GARZA: Other points or comments? Dr. Dwyer?

DR. DWYER: I wonder if we could have more elaboration on this decision tree approach.

DR. GARZA: Let me hold off on that one for just a bit. A related question, Dr. Hansen, that perhaps you could address.

In terms of premature infants that are

born at 400 or a 1,000 grams and then come to be included in these studies, most of them will come with significant growth deficits at that point.

What sort of confounders do you think we ought to be aware of when we take children that, in fact, are premature, have incurred a growth deficit, and then are put on formulas and compared to children that are term and do not have the same growth potential?

Because, in fact, one can see much greater efficiencies in growth in the face of growth deficits because of catch-up that we don't fully understand.

DR. HANSEN: Well, there's not only the differences in the more SGA or the growth deficits that you're talking about in the --

DR. GARZA: I'm just talking about the AGA, that incurs a growth deficit.

DR. HANSEN: Iatrogenically?

DR. GARZA: Iatrogenically, under medical care, which is the norm, because we don't understand the nutritional needs of the 400 grammar

as well as we should.

DR. HANSEN: I think that is a good point. There's that issue where we're beginning to feed pre-term infants because we're not able to -- we don't fully understand how to help them keep up to where they would have been had they stayed in the womb. They tend to fall off and get behind and then they have a period of catch-up, if you will, hopefully they have a period of catch-up. Often they don't make it, but they do show some accelerated growth.

In any event, even the physiological growth rate is significantly higher in the pre-term infant than in the term infant. So it makes them a different process, as well.

A pre-term infant will double -- well, depending on the age you pick, but a 26-week pre-term infant in utero will double their weight in a month. A pre-term infant born at 400 grams will double their weight in about two months. A term infant doubles their weight in about four months to six months.

So the rate of doubling weight or the growth rate is significantly different in the pre-term population.

How that impacts on generalizability, I think it has a big impact potentially on levels of nutrients. I don't know how big the impact would be on qualitative presence.

I think another thing about pre-term studies is they tend to be shorter in terms of exposure. Term studies are four months feeding minimum and many of them go out to a year. So you have the opportunity to observe for effects longer in the term infants.

It doesn't have to be that way, but that's just the way that it is often done.

DR. GARZA: Two other related questions. How well do we understand the body composition that is gaining catch-up in pre-term infants and how is that influenced by the rate of catch-up and what are the longer term consequences of various rates of catch-up?

DR. HANSEN: That's a very complex

scenario. I think that is just beginning to be addressed in nutritional circles. We only recently have the DEXA techniques to look at body composition and some people don't feel comfortable with those, even in pre-term infants now.

But even measuring body composition in the pre-term infant is very difficult and the body composition of the catch-up is different. Premature infants are born with much less subcutaneous fat, much smaller fat stores which accumulate, and, clearly, when you see a chubby newborn term infant, they have a lot more fat on board.

So their body compositions are different. They are changing. I don't know what the impact of the various nutrient interactions and so forth might have on that, but those are all physiological differences.

DR. GARZA: So the body composition of the weight gain that's supported by the formulas may be quite different in the term and pre-term.

DR. HANSEN: I think that's probably

reflected in the composition of the formulas. The pre-term formulas have much higher protein content. So the protein-calorie ratio is 2.7 to 3 grams of protein per 100 calories, reflecting the rapid growth needs for lean body mass of the pre-term infant, but still they accumulate fat at the same time.

So how you achieve the body composition that they need requires a different formula for the two different populations.

DR. GARZA: Would any other of the speakers want to address any of these questions?

DR. SIGMAN-GRANT: Are drug-nutrient interactions taken into account during pre-term trials? Because I would assume that many of them may need drugs. The other question is when the clinical trial protocols, are 30-week gestational babies compared in a group with the ones who are born earlier?

So that when you follow them out, are they segmented when you look at them? Do you start at 30 weeks and everybody in the clinical trial starts

at 30 weeks gestation? Can somebody explain that?

DR. GARZA: Dr. Hansen discussed how they do it at Meade Johnson. I don't know whether others would like to address that question. The range of gestational ages that are included generally in clinical trials and the degree to which they are subdivided.

DR. SIGMAN-GRANT: Right.

DR. CARLSON: There was a first question, but I didn't hear the first question.

DR. SIGMAN-GRANT: The first question was about drug-nutrient interaction. Is anything taken into account in the analysis?

DR. CARLSON: Growth and nutrient interactions?

DR. SIGMAN-GRANT: Drug.

DR. GARZA: Drug.

DR. SIGMAN-GRANT: Drug and nutrient.

DR. CARLSON: Drug and nutrient interactions. Okay. I can only speak in our own clinical trials. I have done three pre-term clinical trials in very low birth weight infants.

They ranged in age from 26 to 32 weeks gestation.

We generally stratified the children in weight ranges. I didn't necessarily do that in the first couple, but in later studies, we realized that's an important thing to do to make sure you get randomization, so that you have your groups as similar as possible.

As far as drugs, generally, in most of the clinical trials that I am aware of, even in my own, where they were relatively small infants, we, again, looked for the healthiest babies in the unit, because we're not interested in studying disease and drugs and so on. So we try to get a population of infants that can tolerate oral feeding within the first week of life and are relatively rapidly on a 120 kcal per kg. Certainly, by the first three weeks of life we like to see that, and, generally, these are not the children who are getting huge amounts of drugs or a lot of intervention.

DR. SIGMAN-GRANT: Can I just clarify about the --

DR. CARLSON: But I completely agree.

DR. SIGMAN-GRANT: You stratify by weight, but not by gestational age.

DR. CARLSON: We actually stratify within weight categories, but I have never had a study where the gestational age was not the same in both groups. The mean always -- if you do that, you have a range, again, within your population.

DR. SIGMAN-GRANT: Is there a great deal of difference -- this is my ignorance, I'm sorry. Is there a great deal of difference physiologically between a 26-week and a 32-week?

DR. GARZA: Yes.

DR. CARLSON: In my experience --

DR. SIGMAN-GRANT: So when you say a range, and that's the range you give, could there be differences within comparative groups?

DR. CARLSON: Yes. Within the group, there's going to be variability. But what you are trying to design in a clinical trial is to make sure that variability is the same in both groups, because, in effect, you are trying to compare an

intervention or some experimental intervention.

So I don't think you can eliminate all variability, including all physiologic variability. I think maybe the question you're sort of getting at here is, is the nutrient composition -- to me, this is the relevant question, is the composition of the nutrients that are being fed in those situations meeting the physiologic needs.

If I were to address that, I think I would say that the formulas that we have used and other people use in trials are nutrient enriched formulas designed for pre-term infants, have a range of nutrients that are, to the best of everybody's knowledge, the nutrients these babies should be getting, in the range they should be getting, as a backdrop.

DR. SIGMAN-GRANT: My question is, and then can you generalize that to the term infant.

DR. CARLSON: Generalize the nutrients?

DR. SIGMAN-GRANT: The composition of the formula that's being fed.

DR. CARLSON: Maybe I'm not saying it very

clearly, but what I'm trying to say and I think what I hear all the other speakers saying is that maybe yes, maybe no. It depends on the nutrient.

DR. SIGMAN-GRANT: Thank you.

DR. GARZA: Susan, before you leave there. Are there any follow-ups to Susan's response? There is an important point that I thought Dr. Sigman-Grant was making, and that dealt with the distribution of gestational ages within comparison groups, because, in fact, you can hide a lot of sins by saying that the range and the mean are the same, without looking at the distributions of the physiological ages between or among your various groups.

DR. CARLSON: Exactly.

DR. GARZA: How stringently are those distributions controlled in clinical trials and in your opinion?

DR. CARLSON: Well, I don't know of anyone who has controlled within gestational age. We are usually looking for the baby between 800 and 1,500 grams and that is why we -- usually, if we do

stratify, we do it within weight categories, because we want to make sure there are the same number of babies between 800 and a 1,000 grams as there are between 1,250 and 1,500.

In general, I think most people think that that weight makes a difference. I personally would rather have a 1,500 gram baby than an 800 gram baby. I think that's pretty obvious. But do we feed different formulas to these babies? The answer is no. The standard for a backdrop of an intervention would be a nutrient enriched formula that has, admittedly, higher levels of nutrients than term formulas, and that's because of scientific studies that showed that those are appropriate.

DR. GARZA: Thank you. Dr. Lien?

DR. LIEN: Just to further reinforce what Dr. Carlson said. The stratifications are such that, between formula groups under study, experimental formula and control formula, the stratifications by weight will contain essentially equal number of infants per weight range.

Let me also, again, return to the question before the panel regarding pre-term and term data, whether we can generalize data from pre-term infant studies to the assessment of term infant formulas.

It is essential to realize, again, that I think you have to take this on a case by case basis. You can't generalize all pre-term data. But if you look at the nutrient that's well absorbed and digested in pre-term infants, you understand that, you understand something about its metabolism in the pre-term versus term, and then you look at the pre-term study population very carefully, and, again, this has to be stressed and we've just been a few minutes discussing this.

I think that is the question before the committee.

DR. GARZA: Thank you. Dr. Caplan?

DR. CAPLAN: I just wanted to clarify an answer on the drug-nutrient interaction question a little bit further, which is that I think there are, in neonatology, some very important drug-nutrient interactions.

The ones we see most often are steroids and diuretics that markedly can affect growth and absorption of various nutrients. I think in most of the clinical trials that have looked at formula supplements, et cetera, they have all used those as exclusionary criteria.

So I think we can -- although they exist, I think at least in the studies, they've corrected and removed that risk.

DR. STALLINGS: Sort of as a follow-up to that, though. What it does leave -- and I was going to comment that most of the published literature certainly doesn't show that there is any statistical analysis, one, because they are either uncommon events or they are excluded.

So we don't have much data on infant formula in the setting where the babies are the sickest, because by design, currently, those are excluded.

So as you get sicker and as you get younger, I think we have -- and, certainly, correct me if I'm wrong -- we have fewer and fewer data,

because of the nature of the design of the clinical studies we have been conducting the last ten years.

DR. GARZA: Are there any other questions from the advisory committee?

DR. DENNE: I have one other.

DR. GARZA: Yes. Then we're going to come back to the decision. Thank you. Scott?

DR. DENNE: I just had a comment and a question. All these studies in pre-term infants, by necessity, are done under a medically supervised environment. They're all done in the hospital.

That has a lot of implications, not the least of which is that nutrient intake is controlled by the investigator for at least a significant portion of the study.

I was wondering how any of the speakers might comment on how that would affect the generalizability of the results to term infants.

DR. GARZA: You want to take that one, Dr. Hansen?

DR. HANSEN: The end of that threw a curve to me on the generalizability. What we try and do

is clearly randomize so that when we're doing, for example, a multi-center trial, that the practices of one institution are randomly distributed among the different formula groups and, similarly, in the other institutions.

So that from an intervention perspective, at least the effects that are being seen are looking at the intervention to see if there's a difference between the two formulas. They should be the same in the randomization, and that also applied to drug interaction; what drugs we don't eliminate.

We do eliminate steroids, for example, because we know they stop growth and growth is a very important parameter. So we do eliminate those, but for other potential drug interactions, theoretically, the drugs are going to be randomly distributed among the group, both groups.

So looking at the difference between the feedings would still be relevant, because it's controlled for hopefully in the randomization.

DR. DENNE: Let me just clarify. What I'm

saying is that pre-term studies, that we control the intake, and term studies, the term baby controls its own intake.

DR. HANSEN: Exactly. When you put that at the end, when you talk about the generalizability part of it, that would raise, to me, questions about generalizability to the extent that that might be a factor in terms of the extent of growth that might be occurring.

DR. GARZA: Dr. Dwyer? Then we'll come back to you, Dr. Lien.

DR. DWYER: It was the question about decision tree.

DR. GARZA: We're going to be coming to that. Dr. Lien, then we're going to go to Dr. Anderson on the decision tree.

DR. LIEN: That's fine. If I could just address the question on the floor. We know from the studies many years ago, from Sam Fulman and the Iowa Group, that term infants tend to control their intake based on the number of calories, not on the volume of formula. So that term infants will drink

to a relatively constant volume, constant caloric intake.

There is certainly variability within that and LBW studies are more tightly controlled, as you indicated, than term studies would be.

On the other hand, what that means is that your variability in the assessments, for instance, growth, are more tightly controlled. Your standard error should probably be less in a pre-term study if you're looking at exactly the same population of infants compared to a term study.

The other component of this is if you are to consider high dose, high level intake nutrients from term infants, you would be forced to look at the few outliers that might be consuming a 1,000 or 1,200 mls per day.

So the means will be more variable. You'll probably have the same mean between groups and you have a lot more variability possible in the term intake, due to variabilities in nutrient intake. I'm not talking about other issues related to population.

So I think actually the pre-term study where you are closely controlling nutrient intake gives you additional power to develop the possibility of statistical differences between groups.

DR. SIGMAN-GRANT: I would just like to say something to that. Breast fed babies may indeed determine -- full-term breast fed babies may indeed determine volume and intake. Formula fed babies, the determination of volume and intake oftentimes is determined by the care giver and many times over-feeding is seen.

So that's not necessarily true what you said, because oftentimes formula consumption is higher in term infants.

DR. GARZA: There is some data now that show that, in fact, the variability, the day to day variability in formula fed infants is exactly the same as it is in breast fed.

Susan, we're running out of time. So I'm going to go ahead and deal with the decision tree.

DR. CARLSON: Could I just say one quick

comment, though? I want to remind everyone that all pre-term studies are not the same. There are pre-term studies that are only done in the unit. There are studies, like we've done three studies where we fed the agent for the first 12 months corrected age, and the children we definitely ad libitum feeding.

DR. GARZA: Thank you. Dr. Anderson? Is she still here? Dr. Dwyer wanted to hear more about the decision tree.

DR. P. ANDERSON: Johanna always asks those good questions. Decision tree approach, in this particular scenario, is very multi-faceted. What we tried to do was to present our thinking that went into our decision-making in any of the particular areas of concern.

So what we did is we broke it down into specific types of nutrients and ingredients and then we also broke it down into the type of study that would then be conducted or had been conducted.

So in each particular instance, there are different questions that pop up, depending upon

what particular study you want to generalize the findings to from pre-term to term, or from one population to another population.

There are always different questions that will come up. It is very hard to come up with a computer algorithm to take you through each step in the thinking.

What we have tried to do, though, is to present here some of the questions that we do consider.

DR. GARZA: Was the decision tree specifically in your handout to the committee?

DR. P. ANDERSON: No, it was not.

DR. GARZA: Could you make that available?

DR. P. ANDERSON: I guess what I'm trying to say is the thinking that went into a decision tree, and, in fact, we have talked about this a lot in our medical department, as to whether we could contrive a tree of thinking, it's not something we've necessarily sat down to do, because most of ours are discussions based upon emerging science and it's continually evolving.

DR. GARZA: So you're suggesting that as a concept rather than as a tool that you presently have.

DR. P. ANDERSON: It's a concept at the moment and I would be very happy to help and develop something for the committee to move them forward in their thinking. We at Ross would be happy to do that.

DR. GARZA: If you had it available. That's fine. Thank you.

DR. DWYER: I just wanted to say that I find these trees helpful.

DR. GARZA: Except one doesn't exist. They would offer to make one for you.

DR. DWYER: Well, perhaps we could get Dr. Yetley to do one. She did a good one for significant scientific agreement and she's got time on her hands now.

DR. GARZA: We've got a few more minutes. I indicated to Dr. Gelardi that if we had a few more minutes, he could come back to us. I don't know whether he's still in the audience or not.

DR. GELARDI: I am.

DR. GARZA: Do you have anything else you want to add, Dr. Gelardi? We have about three minutes.

DR. GELARDI: We really appreciate the opportunity. I said that earlier. I think it is extremely important that we all work together, meaning the industry, the FDA, the expert panels, so that we can hopefully provide the very best science and truly meet the needs of the individual.

The infant health is at the core of what I think we all are trying to address. When I stopped, I was trying to get to the point with respect to generalization of clinical study findings and we've obviously had further discussion on it. So some of this perhaps you've already, in essence, heard, but I would like to kind of give an overview.

Any generalization of findings from a clinical study in one population or other populations in the absence of specific clinical data should be reviewed on a case by case basis for

specific merit and relevance.The FAC has been asked to discuss the scientific issues related to the generalization of findings from a clinical study and we believe it's important to recognize that there is no definitive answer in the issue of generalization, and there are, for example, cases where or instances where the data are not relevant.

I think you already heard some of that. There also are cases when data may be informative, but not definitive.

However, there also may be circumstances when data from a study are very applicable and, therefore, can be appropriately extrapolated to another formula in an infant population.

In a way, I appreciate the interruption because I think the commentary in between has underscored that point.

Any extrapolation of data, we believe, must be justified by generally accepted scientific principles and be reviewed for scientific merit, while meeting the applicable legal standards; for example, the classes of compounds, the source of

ingredients, the intended use, and bio availability.

Additionally, each situation must be examined on a case by case basis has been underscored and an informed decision made on the basis of the relevant science.

We had one example that I would like to provide. Some of the other aspects were discussed. But for example, with respect to bio availability, a nitrogen balance study in pre-term infants showing absorption of a protein source could be expected to be applicable to term infants.

However, the mechanism of absorption for some nutrients differs with age, and, again, for example, calcium mass balance versus Vitamin D dependency.

In addition, there is recent evidence that trace elements may be more absorbed by premature infants. In these situations, the results from the pre-term study would not be applicable to a term infant formula.

We're saying this is a complicated area

and there's a lot of information that needs to be examined and looked at again based on the good science, experience, and the expertise, and it would be hopeful, from the industry point of view, that all of this could be done in a thorough process.

One of the things that I mentioned earlier was that based on the best interest of infant health and on good science, the Congressional intent that came both in 1980 and in the 1986 amendments, and I was intimately involved back then. I earned my gray hairs, I guess.

But I have been involved since then and the Congressional intent and FDA's understanding and agreement was that there would be a pre-notification and not a pre-market approval, and, indeed, when Senator Hatch made a comment, he noted, and I quote, "I also agree with the FDA, the pre-market approval is not desirable in this instance and understand that the procedure is not intended to become a precursor of such FDA actions."

I was involved with both Senator Gore and also with Senator Metzenbaum in terms of some of the interchange before Congress, where they specifically identified that it was important to have improvements in infant formula and that they did not want to stand in the way with regard to assuring that there were these changes made that could indeed make the formula such that infants' health would be benefitted.

DR. GARZA: Thank you, Mr. Gelardi.

MR. GELARDI: Thank you.

DR. GARZA: We also have three minutes, if there's anyone else from the public that wants to make a comment.

Given that Mr. Gelardi was given additional time, is there anyone else in the audience that wants to speak?

DR. DWYER: Dr. Garza, I wanted to raise a question, since we have many experts here who may not be here later.

It's back to this issue that was addressed by several people. I think Dr. Thureen addressed

this issue of the number of small babies who are around to be looked at.

The question is that whenever you tighten the criteria in terms of gestational age or birth weight or health or whatever, it means that fewer cases are available in any one clinical setting. This being said, more hospitals or clinics or practices are going to need to be used to study to make the power adequate for study.

And the problem that I see there is that it also means that any differences within institutions, between institutions, you randomize within the institution and assume that everything else is going to be controlled.

But if there are differences between institutions, then there surely are with premature infants. Dr. Doug Richardson at Harvard Medical School and the Boston Beth Israel Hospital, Deaconess Hospital, whatever it's called now, has certainly showed that.

It seems to me this is very troubling. So it's a tradeoff, and I wondered if anyone had any

solutions to that.

DR. GARZA: You think that the larger centers then, given the randomization process, would not -- may over-influence results because of their particular practices?

DR. DWYER: No. I think the issue I'm thinking about, going back to some of Dr. Stallings' comments to us, that you lose something whenever you add another institution.

Certainly, you lose a great deal. It becomes more complex. But there are also these differences, particularly because the premature infants, as you go down in gestational age, is very sick, as Dr. Stallings indicated. A lot of them are very sick.

So even if you select the same exclusion criteria across institutions, there are all these other things that are not included in the criteria for inclusion or exclusion that differ between institutions, at least in my limited experience.

DR. GARZA: Dr. Hansen, I think, is willing to address that.

DR. HANSEN: Clearly, the best thing to do would be to do it at one institution, but doing one of these studies at one institution with adequate numbers to get results would take ten or fifteen years. So that's a real problem.

We do the best that we can and we put in the institution as a covariant in the analysis. So that, hopefully, as much as you can statistically adjust for such things, the effects, the main effects of the treatment are accounted for in the analysis of covariance that goes by including the institution or the site as a factor, and, indeed, we do find some differences.

Hopefully, we don't find that they are way outside, an outlier kind of thing. That could be troubling for us. But in a matter of practicality, that's what we have done to try to approach for it at Meade Johnson anyway. I imagine the others do the same thing.

DR. GARZA: Dr. Giacoia.

DR. GIACOIA: I have a question. In the very tiny premies, what is the variability at age

of enrollment?

DR. HANSEN: Variability in?

DR. GIACOIA: Age of enrollment to the study.

DR. HANSEN: At the age of enrollment into the study. The way we randomize, and I imagine it's similar at the other companies when they do theirs, we take the weight groups, the weight classification.

We have one randomization table for that weight classification, have another randomization for the other weight classifications.

So each one is independently randomized within its weight classification and we block the randomization such that after you complete four or five, depending on the number of groups, but after a small block, you've got all groups represented to increase the chances of having equal representation.

DR. GIACOIA: Within the strata of the very tiny ones.

DR. HANSEN: He's asking the variability,

and I don't -- do you have an answer for the variability, the range?

DR. STALLINGS: You mean variability of gestational age around a birth weight?

DR. GIACOIA: Post-natal age at enrollment.

DR. HANSEN: Post-natal age.

DR. GIACOIA: In the very low birth weight infant.

DR. GARZA: In other words, your expectation would be that a 1,000 gram infant is likelier to be enrolled when his post-natal age is six weeks, while the 400 gram infant may not be enrolled until the baby may be eight, ten weeks, that the variability co-varies with -- or varies in some way with initial gestational age.

DR. HANSEN: From our perspective, we have observed that. But what we do when we do our statistical analysis, we have shown that by stratifying the way we do, that the mean gestational age, the mean age at introduction is generally not different.

I mean, it's not different among the treatment groups. Now, they will be different if they are less than a 1,000 grams versus greater than a 1,000 grams. The greater than a 1,000 grams will be younger at age of enrollment versus those that are less than a 1,000 grams.

But between treatment groups, we, in general, find that just the randomization has made them so that the age of enrollment within that treatment group is -- between treatment groups is not different within a strata.

DR. CARLSON: I was just going to say that the post-natal age does vary in the studies and just within our own three, our first one, we waited until infants were on full enteral feeding and 120 kcals per kg. So they were, on average, three weeks of age.

In the other ones, we enrolled them when they were a week of age. So they had to be on enteral feeding.

I think some studies have -- I think there's been quite a lot of variability on this.

The only point I would make is how does this affect anything, obviously, you're more likely to achieve the null hypothesis on growth if you're doing this very randomly.

And I didn't speak to that in my comments on growth, but it is actually a legitimate question. Are the few studies that have found growth effects, for example, on the LC PUFA, in very low birth weight babies, is it because they were extremely well controlled, done in one center, everybody was started at the same age, they weren't -- those are legitimate questions.

But I think as I understand the issue today, what we are talking about is when you do find an effect that's adverse and you have adequate power in the pre-term baby -- I apologize.

When you do have adequate power to conclude there is no adverse effect, which includes all of these issues we're talking about today, including adequate number in the group, consistent enrollment, single center, if possible, and you still can't find an effect on growth, can you then

extrapolate from the pre-term baby to the term baby, and I think the answer to that seems, to me, pretty obvious that there shouldn't be an issue.

DR. GARZA: Dr. Buchanan?

DR. BUCHANAN: Thank you, Dr. Garza. In listening to the discussions and the questions that have taken place around the table this morning, a lot of them seem to have to do with statistical principles and statistical designs.

I would like to offer, we do have a statistical staff on hand that would be available if you need to have some additional resources during your deliberations in terms of principles of statistics or specific applications.

So, again, I don't want to comment on any of the proceedings. I just want to make that resource available to you if you need it.

DR. GARZA: We will consult with Dr. Anderson and see whether he thinks that might be helpful. But we will be turning to him quite a bit this afternoon on some of these issues.

DR. THUREEN: I am not sure if this is an

appropriate question to address now, but I'd be curious, for members of the industry, if the decision is made that, in some cases, on a case by case basis, it needs to be decided whether or not data is extrapolated both from one group to another, who should be making the decision as to whether or not it's extrapolatable?

Should it be done in-house at each particular company? Should it be done with an advisory panel that is set up for this reason? How should that be handled or how would you envision seeing that handled?

DR. CLEMENS: Typically, those kinds of situations are addressed --

DR. GARZA: Go ahead, Dr. Clemens. Then we will hear from Dr. Lien.

DR. CLEMENS: Eric, do you want to go ahead first?

DR. LIEN: No.

DR. CLEMENS: Typically, those kinds of situations are considered right at the front by the statistical design and by the statistical design

team. So the issues about extrapolation is already considered.

DR. GARZA: So they're doing it internally, in-house.

DR. CLEMENS: Whether it's a major institution or by the manufacturers themselves, but, therefore, they design the study. It is done blindly, so none of the investigators know, and consumers know, so that the extrapolation issue is already addressed.

DR. GARZA: Dr. Lien?

DR. LIEN: This will depend on the nutrient under consideration, but we do, and I believe the rest of the industry will use consulting advisory boards quite liberally.

It is very important that we not arrive at decisions by ourselves, but we talk to the most informed medical professionals that we can avail ourselves of.

So it's quite common under these circumstances to convene a whole series, possibly one or more, advisory boards to discuss the issues,

to lay them out quite openly to advisors.

There might be examples where that does not happen, but there are certainly many examples where it does.

DR. GARZA: Dr. Anderson?

DR. J. ANDERSON: I wonder if someone could say something about the process by which this occurs. For instance, suppose that we are in a situation, as we're discussing, where a study is done in pre-term infants with the plan to use the information for approval for the use of some formula in term infants.

How does that go through the pre-market notification process and at what step and by whom besides the judgment made is correct or incorrect?

DR. GARZA: Chris or Beth?

DR. LEWIS-TAYLOR: Under the statute, manufacturers are required to submit data to provide assurances that they have met provisions of 412.

I think it is fair to say that in our proposal, we attempted to outline what, from our

perspective, appeared to be a reasonable approach. That proposal is not final. So I speak in context of that.

Clearly, what happens is that data are submitted to the FDA staff. The FDA staff examines the data, are allowed to ask questions. There is sometimes a dialogue back and forth. And then either the agency objects to the assurances or finds no reason to object to the assurances.

DR. J. ANDERSON: And if the agency objects?

DR. LEWIS-TAYLOR: If the agency objects, there is no provision that prevents a manufacturer from going to market over the agency's objection. It's not in the statute. I think it's fair to say that it's a responsible industry that's interested in making sure they do meet it.

DR. J. ANDERSON: And that's the way it's different from pre-approval.

DR. LEWIS-TAYLOR: Right. We are not talking about a pre-approval process that's a go-to-market or no-go-to-market. It's to provide

assurances which it's desirable to have the agency not object to.

DR. HEUBI: I know there was a limitation of time and I think while the industry representatives are still here, it would be worth getting their comments, because one of our charges was a discussion about disease states versus normals and generalizability and what approach might be taken in that context.

As a pediatric gastroenterologist, we deal with a variety of these "specialized" formulae that are out there and the issue really, in my mind, is how should we address the issue of generalizability of products that are currently available or proposed in some kind of guidelines we might suggest.

DR. GARZA: Would any of you like to address that question? I suspected as much.

DR. HANSEN: One thought comes to mind, and it doesn't have to do specifically with pediatric gastroenterology, but it may deal with inborn errors of metabolism.

Products for inborn errors of metabolism, many of those conditions are so rare that it's virtually impossible to do a significant duration study or you'd have ten to fifteen years go by before you had enough patients to really test the formula and so forth.

So one of the approaches that I think is reasonable would be to convene an expert panel, as has been suggested, of people who run metabolic clinics who handle those specific diseases, where you have a formula to be tested, and say what would be a reasonable test for this formula in this situation.

To me, that's about the only way you could really come up with a way to adequately or appropriately test for a small -- a product that's intended for a very small population, for which you would have to test the entire population in order to virtually have enough to test by the usual standards.

I don't know if that was getting to anything you --

DR. HEUBI: I guess one of the questions I have is we now have this burgeoning population that appears to have allergic disease that we're dealing with on an ongoing basis and the application of amino acid based formulae that we know nothing about growth or anything in that population that would be of value to know in terms of understanding whether it's appropriate to be using these agents for long terms in these patients, other than the fact it's a practical application.

DR. GARZA: Would you identify yourself?

DR. EULER: My name is Art Euler. I'm a pediatric gastroenterologist and I've done a few --

DR. GARZA: And you are here representing yourself?

DR. EULER: I'm here as a public citizen.

DR. GARZA: All right.

DR. EULER: To specifically address what Dr. Heubi had, I think the best example would be to look at formulas that are used in kids that have what might be called allergies to cow's milk protein and allergies to soy protein.

I think one of the best examples of how that should be approached is an Italian study where they actually followed those kids for a number of months. I don't think you can extrapolate from studies in normals.

If you were to feed -- I mean, and kids will grow. Normal kids will -- term infants will grow on protein hydrolysates. There is no question about that.

But whether that is extractable to a diseased population, I think, is debatable. So that if one has a protein hydrolysate and it is to be used particularly in the population such as infants that have protein intolerances, I think you have to do specific studies in that population.

DR. GARZA: Thank you. Are there other questions from members of the committee? Dr. Anderson?

DR. J. ANDERSON: I wonder, since there are actually -- well, depending on how we count -- three or five questions before us and we haven't heard much from our speakers regarding the issue of

how to deal with differences in adverse events, wherein attrition rates, whether any of them want to say anything about those before this part of the program is ended.

DR. GARZA: Would any of you like to address either of those issues? Susan? Go ahead.

DR. CARLSON: I was actually relieved I didn't have to try to answer these questions, but I'm going to try.

The last two questions. Is it appropriate to conclude that a new infant formula supports normal physical growth under its intended conditions of use when there are differences in adverse events between the test and control groups which raise clinical concerns, but the study wasn't powered to detect any?

Okay. Well, I've been a victim of this, so that's why I came up here. I don't think when something is -- we all know there can be exuberant positive and exuberant negative results, and I have come, after 20 years, to the view that this is why you get an outside monitor on safety from the get-

go and that's what I do now, and that person has the data feeding into them.

I think there's a great danger of concluding, before you have adequate power, that things are working or not working, and especially on the issue of safety. You could get three kids that develop NEC right at the beginning of the study, random, never get another one in the next hundred.

So I think it is extremely dangerous to make any conclusions from a study that doesn't have the power to look at safety issues.

On the second point, is it appropriate to conclude that a new infant formula supports normal physical growth when there is a large difference in attrition rates?

Whenever we look at studies, we make some attempt to assess the validity of those studies and we look at a number of things. A lot of those points have been raised today by various speakers and by the panel in terms of the questions.

I think whenever you have a difference in

attrition rate in the study, you can legitimately have questions about the validity of that study.

Whenever we talk about generalizing studies, and you saw that I did this when I looked at the growth studies, I immediately eliminated half of them and said as far as I'm concerned, these are worthless, let's not even talk about them.

So this is what we all do scientifically when we look at studies, is we make some assessment of if it's valid or not and if we don't think it's valid, we don't put it into our process.

DR. J. ANDERSON: I wonder, could you say something about whether or not you feel studies should be large enough to have sufficient power to detect important differences in adverse events?

DR. CARLSON: Well, in clinical trials, we don't do what we call studies to determine safety. I've been told you don't use this language.

I've served on a number of human subjects committees and we dance around this issue.

On the other hand, should you do a study

that has enough -- and the other issue in clinical trials is you power it for some outcome that is your hypothesis. You do not hypothesize adverse outcomes.

So we must design clinical trials to measure something that we think is positive, and we do, and I think, the way I look at it is we're obligated to look for adverse events in the context of that.

Again, I have always done this. I know that all the formula companies do this. And, again, if you find something or even, again, something that's suggestive, it's certainly -- again, if it's not powered to look for that adverse event, you have to take that for what it's worth. But I think it's legitimate to plant a doubt if you've done a trial with a couple hundred people and you see something that's suggested, then I think it's legitimate to look at that.

Whenever we do studies, we -- and I think the new standard is sort of post-market surveillance, looking at your population as you

bring this product into the market and looking for adverse events.

DR. J. ANDERSON: So what would you see the role of post-marketing surveillance to be in a setting like that?

DR. CARLSON: Well, you are not talking to the right person on that. We have experts here, and I can't speak to post-market surveillance. I'm just saying that in the context of once you get a formula that's been fed to many thousands of infants, there are systems in place and I think maybe some of the formula representatives would like to speak to that.

MR. GELARDI: I'd just like to make a general offer that hopefully will be helpful. You've been given questions and all that we have just received, as well, and the industry would be very pleased to use the scientific literature that we have, provide it to the committee, actually research the questions, provide the information.

We haven't had the opportunity to address these specific questions either, but we do believe

that we have significant information that would be of value to the committee, and presuming there is an opportunity after these two days, we certainly would like to offer you our assistance in getting the scientific information that we have available and having that for your use.

DR. GARZA: Thank you. Any other comments from members? Hold on, Jim, because we're running quite late now. I want to make sure that, in fact, there are no other questions from members of the committee.

Do you want to address the same question that was raised?

DR. HANSEN: Yes. Obviously, whenever adverse events occur, we become concerned. The question is, is this different, and you might find three times the adverse events in one group as in the other.

It could be one and three, and yet three may be a trivial number if you had a couple hundred infants, as has been mentioned.

I think the thing I always look at when

I'm trying to consider whether an adverse event really deserves serious further consideration is how does the incidence of that adverse event in this study compare with the general incidence of that adverse event in the general population.

For example, necrotizing enterocolitis in premature infants. We see that. We know it occurs in most nurseries at some time. It's epidemic. It causes some problems.

And if you find adverse events and you have maybe five percent incidence of NEC in one group and eight percent difference incidence in NEC in the other, given the overall incidence of NEC of five to ten percent in the general population, you didn't see anything in this study, in either group, that was outside kind of what the norm would be, kind of like a reference standard curve.

On the other hand, if I had seen 15 or 20 percent NEC in one of the groups, which is higher than the outside norm, and even if it didn't reach statistical significance between the groups, but particularly, if it did, then it would raise some

eyebrows for some concern.

Also, if the adverse event that is observed is in the control group, not in the experimental group, then is that a benefit to the treatment group or not? You have to have statistical significance for that, clearly.

But I am less concerned about the treatment group, certainly, if the treatment group has a lower incidence of adverse events than the control group.

Those are just some observations. In very sticky situations, you can't power studies enough to test for many of these adverse events.

So we just make the observations and maybe there's a post-marketing way to get at it, but that's not immediately apparent either.

DR. GARZA: Thank you very much. I want to thank the six presenters. Obviously, the discussion was quite useful to the committee.

I also want to stress that the option that Mr. Gelardi offered this committee is openly certainty to any member of the public. You are

free to forward any information to the government and the government will make it available to the committee, as appropriate.

We will reconvene at 1:30. I hope the mics will be on at 1:30. I think lunch for the committee is in Ballroom D. So we will be back here in approximately an hour.

[Whereupon, at 12:25 p.m., the meeting was recessed, to reconvene this same day at 1:30 p.m.]

A F T E R N O O N S E S S I O N

[1:34 p.m.]

DR. GARZA: I would ask the group to take their seats. Let me go over a proposed agenda for the remainder of the time, get the group's feedback, and then move forward based on that feedback.

We have to deal with two major components. One is the first charge we were given, that first paragraph, and then the second, with the five questions, or three questions, as they have been reformulated.

My suggestion is that we spend about an hour to two hours, depending on how the discussion goes, dealing with the general principles, trying to provide some guidance to staff so that, in fact, they can begin to do whatever homework is necessary for our next meeting as we begin to delve into those specifics in terms of general guidelines that are science based, clinical implications, et cetera, as Beth and Chris outlined them.

Then that we begin an hour and a half from

now or so discussing the three questions, continuing that discussion through tomorrow morning at about 10:00, and then trying to come to some consensus on those three questions by 12:00 tomorrow.

That would give us approximately 40 minutes per question, rather than taking one question at a time, because my concern is that we will be forced to be internally much more consistent if we take them as a block at the end of the discussion rather than taking one, taking a vote on its resolution, then going to the next one, and realizing that there were issues that we might have thought about that didn't quite turn out the way we originally thought.

What I am suggesting still runs that risk of ending up there, but it minimizes it, I think, a little bit.

Is that a reasonable way to proceed? I've learned. I was chair of a department for about ten years and someone asked me once if I was the boss, and I said no. And they said, well, they didn't

understand. I looked at them and I said, "Well, I do." And I said, "There's a big difference between being chair and being boss and if you don't understand that, you're not going to be chair very long."

I have some wonderful colleagues around this table. So I would like your suggestions in terms of proceeding this way or in some other.

Let's proceed and we can always change directions if it's not going well. I always maintain the right to be smarter in 30 minutes than I was.

I used to drive my kids wild, because I could change my mind.

All right. Let's begin then, based on the presentations we heard this morning and the very useful question and answer period that followed, trying to go through at least general principles that we may wish to explore in follow-up meetings.

One example of a general principle that came to my mind to get the discussion going is that increasingly, as we think of how science is

evolving, clearly, normal growth remains a necessary criterion.

I don't know whether it's a sufficient criterion. The definition for normal growth traditionally has been accretion of mass. Do we need to think beyond that to what that mass is?

But to begin thinking in terms that relate primarily to physical growth, but also being clear, in our own minds, as to what the implications of that focus may be, is the pattern important, et cetera, but thinking in more general terms, as I get progressively more specific on just one criterion.

We have heard a number of issues that have come up regarding sample sizes, follow-up periods, power. If we can come up with some general guidelines, and possibly we have the COMA report that offers some very good guidance, I think, somebody has obviously thought about this before we have, and that that might give us a way to get started as we look at those principles that were included in the materials we were sent.

So with that very general introduction, who would like to start the discussion in terms of at least the scientific base or basis for those general principles?

DR. THUREEN: May I ask a question?

DR. GARZA: Patti, sure.

DR. THUREEN: It seems like the COMA guidelines really adapted significantly from the AAP guidelines that were published in 1988 and extended on those.

Would it be reasonable to start with the COMA guidelines, which added a few new things, and then see what should be added from there, particularly with regard to pre-term infants, and then just start reading through those guidelines and see if they would be appropriate ones to continue as the basis of this?

DR. GARZA: Yes.

DR. THUREEN: Since a great deal of thought went into that.

DR. GARZA: That might give it a lot more structure, if you wish to do that.

DR. MONTVILLE: I have two questions. One is that the existing guidelines are very specifically about having been developed for term infants, and we're doing a lot of discussion about pre-term infants.

I would also like to raise the question or have it raised at some point about being normal physical growth as grams of mass as the only indices that we're measuring.

That might have been okay for 1980, but we should be able to do better than that now in terms of composition or at least minimally meeting the normal developmental stages, and I would like to hear that discussed.

DR. GARZA: Okay.

DR. THUREEN: I just wanted to add that we think about this all the time and had discussions about it at noon. The problem is that I think we would all choose to use body mass, lean body mass as the standard, but there are very few techniques for measuring that in infants, and that's one of the big problems.

In neuro developmental outcome, often, those types of tests are really well standardized necessarily and many places that would do studies don't have the ability to do follow-up for the duration of time that most people are saying now, one to two years for neuro developmental follow-up.

So you'd have a set of guidelines of where we would like to go and what is actually currently possible.

DR. GARZA: We could get into those, because that could easily occupy at least a week, because those are very important points. Virginia?

DR. STALLINGS: In the interest of another general principle, I think another thing that has changed over the last few years really is about our commitment to study children.

When you read about the history of all of this, there was actually, I think, a sense of avoiding studying children and as an advocate for child health, I think, in fact, we are obligated to study children.

So the issues about design and

inclusion/exclusion criteria, healthy children, not healthy children, are things that I believe we need to face straight on.

Then that goes to some of the other questions, because the only ethical way to do that research, I believe, is to have it very well designed and properly powered. So once we do it, we have some answers and we can move on.

So I would like to put that on the table as a general principle that we're shifting from do as little as possible to design very good science studies, always with the overreaching commitment to protect the children and their families and that sort of thing.

DR. GARZA: All right. Any comments?

DR. SIGMAN-GRANT: I would like to add to the normal growth issue about considering breast fed infants as the standard.

DR. GARZA: Why don't we begin then? I am assuming that most of you or all of you should have the COMA report sent to us. British Code of Arms on the front.

If you turn to page one, it's titled "Recommendations." There are a list of six general principles. We can take them in order and modify them, add to them, omit them, but it may be a way to begin a structured discussion.

We heard quite a number of people address, for example, the first one that says "all modifications." There was some sentiment being expressed by the industry representatives that "all" obviously would not be appropriate. It would be useful to have your views, obviously, on that.

There was even some discussion as to what was a modification and what was not, and whether, in fact, a nutritional assessment is sufficient or whether you look at matrices and assess formulas from other perspectives, other than the nutrient content.

I am assuming that if we say content, that that also assumes issues of balance, bio availability, but perhaps one could be more explicit.

Who wants to address the first one? Is it

a principle that we ought to take or one that we ought to eliminate? Dr. Garlick, do you have a --

DR. GARLICK: When you say assess nutritionally, I would say we have to define what we mean by nutritionally, by that statement.

Essentially, if you are changing your very mind, the component for something which would, be all nutritional principles, be identical, then I can't see why it has to be judged particularly.

The other question, of course, is who is going to judge it; is it the industry itself or do we have a committee who does it or is it an individual who can make those decisions.

DR. GARZA: You would suggest that, in fact, all modifications should be assessed by someone.

DR. GARLICK: I think so, yes.

DR. CLEMENS: We have right now in the statutes in the United States, we have major/minor changes, and I believe Chris, in her presentation, touched base on major/minor changes. Correct me if I'm wrong on that, Chris. Did you address that,

major/minor questions? Does this group understand those changes at this time?

DR. LEWIS-TAYLOR: I didn't quite hear, Roger, but the difference between major and minor changes is in your briefing packets.

DR. CLEMENS: Correct.

DR. LEWIS-TAYLOR: It is articulated there, and there is a difference.

DR. CLEMENS: Clearly, that those major changes require some type of study and the industry doesn't disagree with that kind of approach.

The minor changes, minor adjustments for manufacturing processes and minor changes that are required to adjust for stability issues, even minor changes that might be invoked by statutes, those kinds of changes, based on scientific evidence, as well as food science data, don't require additional clinical evaluation, whether inside or outside, because based on theory and practice, those things do not require additional clinical evaluation.

DR. GARZA: But, Roger, I don't hear that you are disagreeing with the point that Peter was

making in that all modifications are assessed by someone.

DR. CLEMENS: Assessed by someone.

DR. GARZA: Whether they're major or minor. The degree of assessment will differ, but they are all assessed.

DR. CLEMENS: And, Bert, they are assessed by someone, because, required by statutes, again, all changes are required to be evaluated and submitted to the agency.

DR. GARZA: So is there a consensus, in fact, that that ought to be one general principle we ought to keep in mind as we move to the next meeting?

DR. CLEMENS: What connotes the evaluation process may be important. What are requirements or what makes good sense to evaluate the degree of those changes, as indicated by the statutes, but on what criteria should they be assessed.

Clearly, it has been addressed what connotes normal growth. Perhaps we can come to a definition. But what is the checklist in terms of

nutritionally assessed, based on theory and experience, based on analytical data, based on animal models, where do you want to go with that.

So based on theory and practice, and based on the 80-plus years the industry has in this country and perhaps a much longer period of time internationally, these kinds of changes are well documented.

DR. GARZA: Remember, we don't have to come to closure on any of these. All we're doing is flagging those issues that, in fact, have to be -- we wish to follow up in subsequent meetings.

I have been reminded that we all have to identify ourselves. I have been forgetting, along with most of us.

Any other comments regarding at least that general principle?

DR. HOTCHKISS: My own view is that for a variety of reasons, all modifications to an infant formula should be assessed, not just nutritionally assessed, but, rather, assessed in a broader change.

DR. GARZA: I think that's an important intervention, because it does require broader.

DR. DOWNER: I think when we look at nutritional assessment, we're looking at four essentially basic major areas, anthropometrics, biochemical, clinical, and dietary assessments.

And I think I agree to that if there are going to be any changes, that we should -- they should be assessed. I think the degree of assessment, that is important, and the only objective data from the nutritional assessment is the biochemical assessment.

So even at that level, I think it should be addressed.

DR. GARZA: We will come back to this, because it's obvious we're going to have to spend some time thinking through what we mean by an assessment and if we drop it off at just assessed, then nutritional and the other categories will have to be thought through.

What about the second?

DR. CLEMENS: I'll kick it off. In fact,

the infant formula manufacturers review all relevant data. I believe Dr. Carlson made a comment to that effect this morning, that scientifically, they evaluate what's out there, public information, before you evaluate or establish or design a study that is appropriate for a given change, if you will, and those data are all publicly available.

What the companies have are proprietary information, preliminary information, both on biochemistries, stability, those data are not necessarily publicly available data.

They have maybe some traditional toxicity data, but those toxicity safety data are consistent with evaluating the ingredients, whether the ingredient is GRAS or it has gone through a food additive partition, and those ingredients are not even being considered for inclusion in clinical studies without review by the appropriate body of agencies.

So publicly, those studies are evaluated and then the agencies and various companies put