TRANSCRIPT OF PROCEEDINGS

FOOD AND DRUG ADMINISTRATION

FOOD ADVISORY COMMITTEE

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COMMITTEE MEETING

ON INFANT FORMULA

Greenbelt, Maryland

April 4, 2002

MILLER REPORTING COMPANY, INC.
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FOOD AND DRUG ADMINISTRATION

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Thursday April 4, 2002

9:04 a.m.

Greenbelt Marriott
6400 Ivy Lane
Greenbelt, Maryland

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Robert Buchanan
AAP Liaison

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P R O C E E D I N G S

DR. LEWIS-TAYLOR: Again, good morning. I am Christine Lewis-Taylor and I'm with the Food and Drug Administration's Office of Nutritional Products, Labeling and Dietary Supplements.

Welcome to the Food Advisory Committee meeting on infant formula. Thank you very much for coming. We are quite looking forward to the productive discussions we expect to have today.

Before we get started, there are a few housekeeping issues which we will address. In a few moments, Dr. Bob Buchanan from FDA will generally talk to the Food Advisory Committee about some issues relevant to the Food Advisory Committee for a few moments, and then it will be followed by Ms. Linda Hayden, taking care of some administrative issues.

At that point, the meeting will be turned over to the acting Chair, Dr. Bert Garza.

Before I introduce Dr. Buchanan and allow him to make his introductory comments, I would appreciate it if we could go around the head table

and identify those present as part of the Food Advisory Committee or sitting with the committee.

Dr. Buchanan, could we start with you, please?

DR. BUCHANAN: Sure. I'm Bob Buchanan. I'm with the Food and Drug Administration's Center for Food Safety and Applied Nutrition.

DR. GIACOIA: I'm George Giacoia. I'm with the Endocrinology, Nutrition Branch of NICHD.

DR. CLEMENS: I'm Roger Clemens, USC School of Pharmacy.

DR. HOTCHKISS: Joe Hotchkiss, Institute of Food Science at Cornell University.

DR. DWYER: Johanna Dwyer, Assistant Administrator for Human Nutrition, of the Agricultural Research Service, USDA, and Tufts University, as well.

DR. DOWNER: Goulda Downer, METROPLEX Health and Nutrition Services.

DR. DICKINSON: Annette Dickinson, Council for Responsible Nutrition.

DR. BUSTA: Frank Busta, Department of

Food Science and Nutrition, at the University of Minnesota.

DR. DENNE: Scott Denne, Indiana University School of Medicine.

DR. BAKER: Rob Baker. I'm from the University School of Medicine at Buffalo.

DR. J. ANDERSON: I'm Jim Anderson. I'm from the University of Nebraska Medical School.

MS. HAYDEN: I'm Linda Hayden, and I'm retired FDA CFSAN. I will be here today as your acting executive secretary.

DR. GARZA: I was going to try to convince you I was really Sandy Miller, and this is what happens after spending ten years in San Antonio. But I was warned that that probably wouldn't be very believable.

I really am Bert Garza, from Cornell University.

MS. HARDY: Connie Hardy, from the Food and Drug Administration.

DR. STALLINGS: Virginia Stallings, from Children's Hospital-Philadelphia and University of

Pennsylvania.

DR. HEUBI: Jim Heubi, from the Children's Hospital in Cincinnati, University of Cincinnati.

DR. MOYER-MILEUR: I am Laurie Moyer-Mileur, from the Department of Pediatrics at the University of Utah.

DR. THUREEN: Patti Thureen, from the Children's Hospital-Denver and the University of Colorado School of Medicine.

DR. MONTVILLE: Tom Montville, Department of Food Science, Rutgers University.

DR. SIGMAN-GRANT: Madeleine Sigman-Grant. I'm with the University of Nevada Cooperative Extension.

MR. SCHOLZ: Brandon Scholz, with the Wisconsin Grocers Association.

DR. GARLICK: Peter Garlick, Stony Brook University, New York.

DR. YETLEY: Beth Yetley, Center for Food Safety and Applied Nutrition, FDA.

DR. LEWIS-TAYLOR: Thank you very much and welcome, once again. We are really looking forward

to a productive meeting. We obviously have an excellent group of people with us.

I will now turn over the podium to Dr. Buchanan, who wishes to make a few opening remarks, and we'll move from there to administrative issues with Ms. Hayden. Bob?

DR. BUCHANAN: Thank you, Chris. I just wanted to take a minute to, one, express my personal greetings and, also, express Dr. Crawford's and Mr. Levitt's personal greetings and appreciation for you taking the time to help us with a number of scientific issues today.

I did want to take a moment to talk a little bit about the restructured Food Advisory Committee, so that you have some ideas of what has been taking place since the last time we've met.

We have undergone a substantial re-evaluation of our advisory committee and its activities.

We have established a new structure for it. This meeting right here is a meeting of what we call the full or parent committee. It is now

made up of advisory committee members, plus the chairs of our standing subcommittees.

Currently, we have now structured four standing subcommittees. These consist of a Committee on Dietary Supplements, which is being headed by Dr. Johanna Dwyer; a standing Subcommittee on Contaminants and Toxicants, which is being chaired by Dr. Busta; a standing Committee on Biotechnology, that is being chaired by Dr. Archer, and Dr. Archer expressed his regrets for not being able to be at this meeting. He has recused himself from the deliberations today because of some past consulting activities.

We have a standing Committee on Additives and Ingredients, for which we are currently looking for a chair.

The anticipation is that the parent committee and each of the subcommittees, starting now, will meet approximately three times a year and we hope to be getting a schedule out of these meetings to you shortly.

I would also like to note that because of

the large influx of new people that we will be having on the committee and the different subcommittees, we are planning a training program to precede the next meeting of the full parent committee, so that we can get everybody up to a common level in terms of background on advisory committee rules and requirements, et cetera.

Then, finally, I would like to extend a welcome on behalf of the Chair of the Food Advisory Committee, Sandy Miller, who, again, regrets that he cannot be here today, but, like Doug, he has recused himself from the meeting today.

So with that, I would like to turn it over to Linda. You have some housekeeping items.

MS. HAYDEN: Yes, I do. Again, I am Linda Hayden, and I am going to be the acting executive secretary for today.

First, I would like to read into the record the appointment of our temporary voting members.

It reads, "Pursuant to the authority granted under the Food Advisory Committee Charter,

dated November 30, 2001, appointing authority Joseph A. Levitt, Director, Center for Food Safety and Applied Nutrition, has appointed the following individuals as voting members for the April 4-5 meeting on infant formula."

The listing is Dr. James Anderson, Dr. Robert Baker, Dr. Scott Denne, Dr. Bert Garza, Dr. James Heubi, Dr. Laurie Moyer-Mileur, Dr. Virginia Stallings, and Dr. Patti Thureen.

Upon review of the FDA 3410, which is the financial disclosure report for special government employees, we have determined no conflicts of interest exist for these individuals, and this was signed by our director, Joseph A. Levitt.

Secondly, the following statement is made part of the public record to preclude even the appearance of a conflict of interest at this meeting.

Based on the agenda made available, it has been determined that the committee will be addressing general matters only. The general nature of the matters to be discussed by the

committee will not have a unique or distinct effect on any of the members' personal or imputed financial interest.

To preclude even the appearance of a conflict of interest, each member was screened prior to this meeting. However, the following interest is being disclosed so that the public can evaluate any comments made by the meeting participants.

Dr. George Giacoia, of the National Institute of Child Health and Human Development, NIH, was the project officer for an interagency agreement between the National Institutes of Health and FDA. The IHE funded the NIH network of pediatric pharmacology research units to serve as a resource and prepare guidelines for the design and conduct of clinical trials for neonates.

This agreement was canceled by mutual consent on January 28, 2002. With respect to all other meeting participants, and, namely, this would be our public commentors, we ask, in the interest of fairness, that you state your name and

affiliation and any current or previous financial involvement with any infant formula firm.

As you can see, this meeting is being transcribed. When we reach the discussion portion of the meeting, I would request that you please use your microphone and clearly identify yourselves before speaking.

That should clear up all of our administrative matters at this point, and I guess we can turn the meeting now over to our acting Chairman, Dr. Garza.

DR. GARZA: Thank you, Ms. Hayden. Let me add my welcome, and thank you for each of you joining us, because we will have some very important business to try to conclude by 2:00 tomorrow afternoon.

To get us started, Chris Taylor, I was going to say Lewis -- it still doesn't roll off that easily, Chris. I apologize. Dr. Christine Taylor then will give us an overview to get our discussions going. Chris?

DR. LEWIS-TAYLOR: Thank you, Bert. I do

appreciate the opportunity to do a bit of orientation. If I could have the first slide, please, Sylvia.

The topics today that I will cover will be shared jointly by Dr. Beth Yetley, as well.

If I could have the next slide. I will briefly go over infant formula provisions. I'm sure many of us are familiar with them, but so that we're all on an equal footing, I will provide a very brief overview on the provisions and then a brief orientation, at least from FDA's perspective, why we are here and the next steps for the group.

Dr. Yetley will specifically identify the charge to the committee and provide a scientific overview relative to clinical study issues.

If I could have the next slide. Clearly, the starting point for many of the issues that are on the table today is the 1980 Infant Formula Act. The Act came about due to a number of overriding interests on the part of Congress and it included their recognition that infant formula was unique. It was not like other foods. It was, in fact, the

sole source of nutrition for a highly vulnerable population. And for that reason, infant formula warranted a special set of provisions for their regulation.

Next slide. What, in fact, the Infant Formula Act of 1980 did was to establish so-called Section 412 of the FDA regulations, and, as part of that, it discussed components relative to providing for quality controls, labeling, new training requirements, and recall procedures for infant formula.

Next slide. Clearly, by 1986, Congress had felt that the U.S. Food and Drug Administration had not really done quite enough relative to infant formula and there were a set of 1986 amendments. In that, Congress provided for the agency more specific provisions, particularly in the area of GMPs, audits, records, and something known as quality factors.

Next slide. From all of this, both the 1980 Act and the 1986 amendments, it was clear that the intent and the outcome of the Congressional

statute was that infant formula should not only be safe and contain all of the nutrients required to support infant growth and health, but should provide those nutrients in a bio available form to ensure that the infant formula will support optimum infant growth and health.

Today we operate under several statutory provisions for infant formula. They are, briefly, Section 409 and Section 201, which really talks about the ingredient itself and its safety, either its GRAS, generally recognized as safe, or food additive, and it is based on its provision of being for intended use.

Then as I mentioned, in 1980, Section 412 came into being, and that really addresses the issue of as formulated, nutrients are bio available, and the formula itself supports growth.

In essence, 409 addresses ingredient specific safety; 412 addresses the product itself. The manufacturer is to provide assurances that the formulated product itself supports growth in infants.

This schematic is perhaps not entirely complete and perhaps misses a few of the key issues, but I think it gives the flavor for the regulatory world of infant formula. You have the safety of the ingredient for its intended use, and that, in essence, is a set of threshold issues.

Once that safety is established, you move to the domain of formulation, and there you have your set of 412 assurances.

The 412 assurances are impacted by various parts of the statute, the required nutrients, the GMPs and quality controls, and then the quality factors. On this slide, the quality factors are highlighted because in many ways, they are the chief topic of today's meeting.

From 412, you then move on to marketing, and we have put onto this slide the voluntary component of post-marketing surveillance and we do emphasize that, at this point, this is voluntary.

So basically you have a set of threshold issues for safety, which then lead to formulation under 412, providing assurances. Required

nutrients, GMPs, and quality control issues come into play. Today we are talking about the quality factors that come into play.

If I could have the next slide. We are currently operating what is known as a 90-day notification system. A manufacturer who wishes to market a product is to provide assurances to FDA that it has met the provisions of 412 for that marketed formula.

FDA has 90 days to either object to the marketing or to not object to the marketing. FDA reviews the submitted data to ensure that the assurances provided are consistent with Section 412.

I'd like to spend just a few seconds on quality factors, because while it's a term that's been around for 20 years, it's not always a term that is clearly understood in common parlance.

If I could have the next slide, please. At the time of the Act in 1980, the House Committee on Interstate and Foreign Commerce addressed quality factors. The legislative history shows

that they discussed quality factors are pertaining to the bio availability of a nutrient and the maintenance of levels or potency of the nutrients during the expected shelf life of the product.

Other legislative history talks about quality factors relative to the growth of infants during the first few months of life, the fact that that often determines the pattern of development and quality of health in adult life.

If I could have the next slide. In addition to this general concept of quality factors, Congress postulated and recognized quite clearly that science evolves over time and that quality factors were derived from the state of the science.

Subsequently, quality factors can be adjusted or added to as new science becomes available. So they were seen by Congress as evolving over time.

If I could have the next slide. To the extent that it's helpful, I will offer you a kind of mental orientation for quality factors. Most

likely, they are divided into two groups in the sense of nutrient specific, and this harkens back to the notion of quality factors and bio availability.

Currently, we have the protein or the PER measures, which are seen as a quality factor, and there's a dash-dash-question mark because there may be others. At this time, we are addressing protein/PER.

The second set of quality factors is the formulation in its totality, and that harkens back to the concept of healthy growth.

At present, what is in place is the normal physical growth issues and there's another dot-dot-dash-question mark, because there could be other quality factors that evolve over time as the science informs those interested in infant formula and its assurances as the science informs us of other and additional needs.

If I could have the next slide. What we're about today then, the topic of today's discussion is the component of normal physical

growth. It is under the totality of the formulation. It's under healthy growth and it's that particular quality factor.

I think at this point, if I could have the next slide, we do need to make a special note and that is the fact that in 1996, FDA put out a set of proposals for implementing Section 412 of the Act. That proposal addressed good manufacturing practices for infant formula, as well as quality factors.

At this point in time, a final rule for that proposal has not been issued. In essence, the agency is in rule-making.

If I could have the next slide. We are fully cognizant that input from this committee meeting may or may not impact upon this rule. If it does, we are retaining the option of reopening the comment period on selected topics for this rule as needed, and that is an issue I do want the committee to be aware of.

I would then like to move on just to a little bit of our concept of next steps, why we're

here, what we're about, and then turn it over to Dr. Yetley, who will specifically address the charge to the committee.

You do have today a Food Advisory Committee that is supplemented with an ad hoc task force for infant formula. The general plan or the MO or the SOPs, however you want to refer to them, is that today we will do two things. We will begin a general discussion, or we're hoping the committee will begin a general discussion and answer several specific questions.

We will, at the end of the meeting, undoubtedly request that the ad hoc task force hold an additional two meetings in the near future.

If I could have the next slide. The product of these meetings, we hope, will be basically discussion and input focused on general science-based guiding principles relative to the nature of a good study to be used in the context of providing assurances that an infant formula, as formulated, supports normal physical growth.

The use of the product of this committee,

the outcome of this committee, will be to inform the scientific review conducted by FDA staff as part of our normal operating procedures relative to Section 412.

If I could have the next one. So today we envision a general discussion on guiding principles, but with no closure expected. We believe this general discussion is a starting point and we believe it most likely will be continued by the ad hoc task force.

Today, however, we also are asking that the committee address several, five specific questions, and, on those questions, we are asking for closure by the close of tomorrow's meeting. In fact, that is the reason for the full advisory committee to meet today. In order for the work of the ad hoc task force to be useful to the agency, it does have to presented to the full FAC.

So for this particular case, the full FAC is meeting today so that the specific questions can reach closure.

We do recognize that there will be some

freewheeling discussion in the future that will move on, and that's the topic of the next slide, is that the ad hoc task force will be asked for at least two additional meetings, as appropriate, in the near future, and we do want to point out that the members of the standing Food Advisory Committee are certainly welcome to attend these future ad hoc task force and that the ad hoc task force meetings themselves will be public meetings, consistent with the FAC procedures.

We hope that these additional meetings of the task force will focus and complete the discussion on the general principles relative to clinical studies to be used in the context of 412 assurances and that at some point in the future, this outcome will be presented to the full Food Advisory Committee.

I believe that's the end of my slide set, which we hope helps us in orientation. I will now turn the microphone over to Beth Yetley, who will discuss the charge and some of the scientific issues.

DR. GARZA: Chris, before you go. Are there any points of clarification? I have only one. Can you very briefly review for the group the key or more salient points regarding quality factors that emerge from the 1996 Federal Register?

DR. LEWIS-TAYLOR: That's with Beth Yetley.

DR. GARZA: She'll be doing that. All right. Thank you.

DR. LEWIS-TAYLOR: Not that I don't want to, but.

DR. GARZA: As long as we're going to get those specifics from you, that's fine.

DR. YETLEY: I'm not sure I have taken responsibility for all of the tasks that I was given this morning, but if you still have a question after I'm done, Bert, we can come back to it.

What I wanted to do is to give a little bit of background, from my perspective, in terms of some of the scientific issues that are probably, that do underlie the issues that we have asked this

advisory committee to deal with.

Obviously, I am going to do them in a fairly superficial way, given the time constraints, but, hopefully, they will help you to focus and to give some background. We also have quite a diversity of backgrounds in terms of members of the committee. So for those of you that know these areas fairly well, I hope you will bear with us, and for some of those who are newer to this area, hopefully, they are helpful.

The infant formula clinical study issues that are the focus of this meeting really deal with the first step, as Chris has indicated, in a several step process. The first step that we want to start with is to start to elucidate and articulate a set of guiding principles that can be used by industry sponsors of clinical studies, by FDA or third party reviewers of studies by investigators of the studies, that will help guide in the design, the conduct, and the interpretation of these studies.

We need a common basis on which to talk

and to evaluate these studies. They are related to clinical studies in infants and we are focusing initially on clinical study guidelines that will deal with the infant formula's ability to support physical growth in young infants.

We also asking, as Chris has indicated, for some specific guidance relative to how general principles for generalizing from one type of intended use or one type of population to another group or with some of the more common study interpretation issues that we frequently encounter.

Next slide. So I have indicated why we need it. We need a common set of guiding principles, so we can have a common basis for communication and evaluation. We're targeting infant formula. We're intending that these are not sort of to start de novo. There are many, many general guidances out there. If you go on the FDA web page, you can find more guidances than I could carry into this room in terms of clinical study design and guidance, but we're really wanting to augment what is generally out there and to focus

and target specifically on infant formula clinical study issues.

Next slide, please. As Chris has indicated, clinical studies to evaluate normal physical growth when infants consume a particular infant formula are related to the Congressional language relative to assurances for quality factors.

It is important to remember that quality factors, this concept of quality factors is in addition to the other components that make up the infant formula regulatory process.

It is in addition to the ingredient safety that is done under the food additive or GRAS provisions. It is in addition to the levels of nutrients that are required to be added to formulas and are analyzed in each batch of formula before it goes into the marketplace.

So it is something that goes in addition or beyond those particular provisions and it really deals with biological effectiveness, the nutritional and adequacy and safety from a

biological perspective.

Next slide, please. Quality factors deal with each new infant formula and they're really saying that because infant formulas are special, because they're a very vulnerable group, they are sole source of nutrition. There is no room for error. There is no room for getting it wrong.

They're really saying we've done the best we can, we've used the best information and knowledge we have, we just need to make sure that we've got it right. We do not anticipate and do not want to find problems at this point, but it is simply saying these are very complex food products. They reach a very vulnerable age. We have to make sure that we get it right.

Next slide, please. Perhaps to start the more technical discussion, it is useful to look at the model that the Institute of Medicine has used for nutrient function and risk. And I don't know whether I have a pointer, but, obviously, if your nutrients are inadequate to meet the requirement of infants, which is on the left side of that graph,

the risk of harm goes up. The greater the inadequacy, the greater the harm.

If the nutrient intake is high, then the greater the intake, the greater the harm. So there is increased risk if you don't have adequate nutrition and there is increased risk if you have too much nutrition. So what you really want to do is to make sure that the nutrients in the infant formula in the amounts that are present and in -- given the bio availability that you have in that formula, that the nutrients are provided to the infant in this optimal range.

Next slide, please. Now, one of the first problems that you have is that the optimal range may be very large or very small. This shows, for the more recent IOM reports for infants between zero and six months of age, what they have given as the adequate intake amount versus the upper limit.

For some nutrients, they really could not identify a risk. So there's a very large band between adequate intake and upper limit. For some, they have a very narrow band in terms of that

optimal range. For Vitamin A, there's really only about a 200 microgram per day range. Vitamin D, also narrow. For others, it's relatively large. But for many nutrients, we don't know.

So for some nutrients, clearly, the concern is greater than for others.

Next slide, please. Now, let me just touch briefly on why are we interested in normal physical growth. Well, normal physical growth really is a minimal, but very widely accepted and very commonly used measure of overall nutritional status.

It's useful for the very young infant, because of their very, very rapid rage of growth. Even a marginal nutritional inadequacy may result in some growth retardation, and, also, because the only source of nutrition that the infant has is the formula. So, therefore, if there is a problem with the formula, a difference in growth rate is likely to be reflected.

However, while it's useful, it's non-specific. So that's why we have indicated we need

to start looking at other nutrients in future issues. Normal growth does have the advantage of being a routine part of office visits in a non-invasive measure. So it is a minimum, but perhaps not a sufficient basis in all cases.

Next slide, please. Now, when we are evaluating the nutritional adequacy and safety of an infant formula, we really have to take into account the interaction between the host factors and the product factors, because both can affect the delivery of adequate and safety amounts of nutrient to the consuming infant.

What are some of the host factors? Certainly, different groups of infants, as well as different individual infants will vary in their ability to absorb a particular nutrient, to handle a particular nutrient in terms of body burden, to excrete it, and so on and so forth.

So the nutritional and health status, physiological status of an infant, whether it's related to developmental stage or because of a particular disease or health condition, can affect

their requirements and can be affected by the bio availability of nutrients in a formula.

Next slide, please. The product also can result in an altered bio availability of nutrients in ways that are difficult to predict. The net effect of the nutrient bio availability can be affected by the original source of the nutrient ingredient or, rather, ingredients, by interactions among ingredients in nutrients or nutrient-nutrient interactions, by imbalances among nutrients within the formula, by processing changes or by stability across the shelf life of the formula.

So what you come back to in evaluating quality factors is needing to consider, in conjunction, the host and product interactions.

Next slide, please. So then we can come back to this graph I talked about earlier and start to put or try to put some of this in perspective. One, ideally, the delivery of a nutrient from a formula to an infant will be within this optimal range, but the question that then would occur is if the nutrient bio availability in the formula is

altered in some unexpected way, what does that do to the delivery of that nutrient to the tissues in the infant.

If the bio availability is altered and the nutrient intake would have been, say, in the center and goes down to a lower level, but is still in the optimal range, there is probably little concern. But if the level of nutrient was fairly marginal to start with and bio availability is altered, then you run the risk of moving into an inadequate range.

The same can be said of the upper level or the safety concerns. If the nutrient is at a fairly high level and the bio availability is increased, one runs the risk of moving into the high risk area. So there is an interaction between the host and the product, and it is important to know where the host is relative to this range or at least have some assurance that we are still in that range, and it is important to know what happens as new formulas are developed.

Next slide, please. Now, before we get to

quality factors, there is a step in here that is dealt with in infant formula nutrient requirements, and I wanted to just mention this. This particular table, I have taken information from IOM reports. The protein one is from the '89 report, because the new protein reference values are not out. The others are from newer, the most recent DRI reports.

But the adequate intake is the nutrient requirement that the IOM has put forward for the infant zero to six months of age, and this is based on the mean value in breast milk of an exclusively breast-fed infant.

So this is the requirement, and this value is the CFR value for infant formulas. This is the FDA's regulation for the nutrient value of infant formulas.

These numbers are old numbers and I don't want you to focus on the numbers, because clearly that is one of the tasks that we will be looking at later on to revise.

But the point I want to make is that the infant formula requirements have been adjusted

using sound science judgment and whatever data was available to account for differences in bio availability between formula and breast milk, shelf life stability, and other factors.

So you can start with the levels of nutrients that you know are in breast milk. You assume they are safe and adequate. But when they are added to infant formula, it is necessary to make some adjustment to deal with issues of changed bio availability and stability and interactions.

Unfortunately, we don't have much record of the logic that went into these, and that is one of the things we'll be dealing with in the future. But the point I wanted to make is that you start with requirements based on physiological need, but you need to make some adjustments when you get involved in infant formulas.

Now, these steps are done prior to dealing with quality factors. One hopes and one assumes that they are wise, but they do also underscore some of the uncertainties.

Next slide, please. So with quality

factors, now, let's move to those. We're talking about a quality factor that's specific for each new infant formula product and it is the question of given everything else we've done, including having standards for what nutrients and at what levels, did we get it right, when we've reformulated or we've introduced a new processing line, or there has been a new manufacturer.

Next slide, please. So the general charge to this committee is the question of the appropriateness and completeness of a general science-based set of guiding principles for clinical trials used to evaluate a particular infant formula's ability to support normal physical growth in an infant population.

Next slide, please. We assume that these principles need to be based on sound science and we are asking, as I indicated earlier, that you target them to infant formula evaluations relative to assessment of normal physical growth.

We're asking for general principles at this point, just in general, as well as how they

relate to some specific design and interpretation issues, and we'll get into the specifics at a later meeting.

Next slide, please. The first, more specific question we have or are asking, actually, it's the first three questions, relates to the generalizability of results, the appropriateness of the generalizability of results from one -- from a study done in one population to a product that is intended for use in another population or the appropriateness of the generalizability of results from the study done with one product to the marketing of a different product, to a product different in formulation or some other factor, or what often happens is we have a combination of the above.

And for our first example, we are going to take the example of the appropriateness of a generalizability of results from a pre-term formula fed to pre-term infants when the marketed formula is going to be a term formula fed to term infants.

Next slide, please. Again, we're going to

view this from the host product interaction perspective.

Next slide, please. And from the perspective of wanting to make sure that we understand enough the host nutritional requirements, and so we have to keep in mind how different group populations may have different nutrient levels that need to be utilized in order to maintain this optimal range, as well as how do different products, how do the curves for different products overlap.

Next slide, please. We know that there are a number of differences between term and pre-term infants and I just wanted to go through those briefly. We have pulled together here reference daily intake values for pre-term and term infants from several sources.

The pre-term ones come from a 1994 reference. The term ones come from the 1989 IOM reports. But as you can see, based on scientific expertise, pre-term and term infants have very different reference daily intakes for a number of

nutrients.

I've just given a few examples here, but just to show that they do differ quite significantly in their recommended daily intakes.

Next slide, please. We also know that not only did Congress anticipate that we might need different formulas, infant formulas for pre-term and term, but we also know that manufacturers have made different formulas for the two groups of infants, and these different formulas, on the basis of per 100 kcals of formula, also differs, in some cases, quite significantly in the nutrient concentrations in those formulas.

Next slide, please. If we then calculate the daily intake that a pre-term or a term infant would obtain from consuming their respective infant formulas, we see that the total formula intake or the total intake of nutrients from the two different types of formulas by the two different populations also can be quite different, although some of the patterns of differences start to change some.

Next slide, please. Then if we convert these to a body burden basis, which is nutrient intakes per kilogram body weight per day, we can see, once again, that the pattern and the relationship between the body burden of nutrients for the two groups change.

One would appear, it would appear that, for example, pre-term infants could tolerate much higher levels of some of the nutrients than could possibly term infants.

So both the requirements for, as well as perhaps the tolerance of particular intakes are quite different or are likely to be quite different between the two groups of infants.

Next slide, please. So we see, in summary, that pre-term and term products differ considerably when they are expressed on a per 100 kcal basis, and the requirements for the intakes differ depending on how you express it between the two groups.

Next slide, please. So then we come to the specific generalizability question of is it

appropriate to generalize from one population group to another, when you've done -- is it appropriate to generalize results from a study done in one population, i.e., a pre-term population, to another population, i.e., a term population, is it appropriate to generalize results from a study done with a pre-term formula to an intention to market a formula as a term formula, or what is the more common, is it appropriate to generalize when both the population and the product studied differ from that which is intended to be marketed.

Next slide, please. We have other types of similar generalizability questions. We also frequently are asked to evaluate the appropriateness of a study done in health infants to the use of a product with infants that have underlying metabolic or disease conditions, protein intolerances or whatever, or we are frequently asked to use a study done on one formula composition to another formula composition.

Frequently differences will be different levels or types of protein, levels or types of

carbohydrate, and so on and so forth, or, again, the combination issues.

Next slide, please. We had proposed some protocol guidance in our 1996 proposal that I think relates somewhat to this question. We had proposed that the study protocol should describe how the study population represents the population for which the new infant formula is intended. We notice the COMA report dealt with this somewhat by talking about a guideline that all infants in a study should be characterized with regard to factors known to influence the outcome measures.

I throw these out as a strawman to start you thinking about some of the general principles that we might want to think about to deal with study population in intended use conditions.

Next slide, please. We also had in our proposal a proposed guideline that the study protocol should explain how the study addresses the intended conditions of use of a formula. COMA, again, had a similar statement about outcome measures should be defined specifically for testing

prior to hypothesis.

Next. Finally, we had the last set of related strawmen. We had proposed that a study protocol should describe and compare the composition of the test and control formulas. COMA talks about -- we also talked about the study protocol should describe the basis upon which the test formula is appropriate for use in evaluating formula that the manufacturer intends to market, if the test formula is not identical to the formula that is intended to be marketed.

We're not asking you to particularly say yea or no to these, but to throw these out as strawmen to help you think about some of the general principles that might be needed to cover some of these generalizability issues.

Next slide, please. We also frequently have interpretation questions where the study population, the test and control groups in the study population have very different numbers and/or types of adverse events between the two groups, and we obviously are particularly concerned when we see

higher numbers in the test group, although one would also, I think, be concerned about the control group.

But the issue is how you deal with this. Frequently, these studies are not powered to have adequate power to be able to evaluate statistical significance of these differences, but these differences can be quite large, two-fold, three-fold, five-fold, sometimes higher.

So how does one deal with issues of differences in adverse events when the study lacks sufficient power to evaluate them.

Next slide, please. We also are asking you to give us advice on studies where we find problems and large differences in attrition rates between test and control groups. Again, we can see very large fold differences, but the ability to do statistical significance testing is limited, since, in most cases, the studies are not also powered for this particular end point.

Next slide, please. So, again, looking at, as strawmen, some of the ideas that are related

to these problems or these challenges, we did describe or did propose in our 1996 rule that the study protocol describes sample size calculations and the power calculations and the basis for selecting sample size and study design.

COMA had a statement that studies should be designed to include adequate numbers of participants, allowing for possible withdrawals of infants. Studies should be designed to have the statistical power to detect important effects on important outcomes, allowing for possible withdrawals of infants.

Next slide, please. In our proposed plan, we had suggested that the study protocol should describe the plan to identify and evaluate any adverse effects. COMA suggested that arrangements for dealing with abnormalities found during the study should be in place from the outset. The researchers should agree on the definitions of abnormalities, to trigger action when scrutinizing the results from individual participants.

Next slide, please. So in summary, what

we're really looking for is the nature, guidance on the nature or characteristics of a good study to be used in the context of providing assurances that an infant formula supports normal physical growth.

We also have the specific guidance questions and we anticipate this as a first step to looking, and later meetings, and more specific information on specific measures.

Thank you.

DR. GARZA: Before you leave, Beth. I'm sorry. Are there any questions for clarification for Beth, before we move on to a more general discussion? If not, thank you very much.

MS. HAYDEN: I'm not sure if it's for Beth or for whom, but I'm still not clear what are the things that we need to decide on by these two days, as opposed to the general issues.

DR. GARZA: Let me take a stab at it, to make sure at least that the chair is clear.

MS. HAYDEN: So we'll know what we've got to get done.

DR. GARZA: In your packets, there is

something called or titled "Code 3082, Food Advisory Committee Meeting on Infant Formula."

You have questions and charges. The first question is summarized in the second paragraph of the handout and it speaks specifically to the issues regarding the guiding principals that Beth and Chris both outlined, which have to do with what should be the science-based, what should guide clinical studies, and specifically focused on a formula's ability to support physical growth.

The second question is the third paragraph, with a series of specific questions under that that have to do with the generalizability questions that, again, Chris and Beth raised.

It says charge and questions. You were sent this and they are also in your packet. Do you all have them now? No. Maybe that's where we need to start.

Who does not have or has ever seen? That's the same thing. Charge and questions. The first paragraph starts, "This Food Advisory

Committee is being asked to comment." That's the first sentence.

The first question is the second paragraph and it relates to those guiding principles that have to do with the science-based, the clinical-based, with a specific focus on physical growth.

The second question is the third paragraph, and then that subdivides it into five specific questions. The first three really speak to the larger theme of different populations, different formulas, combination of both, the slide that Beth presented, with the fourth and fifth then addressing issues of power and attrition.

Those are the specific questions that we're going to be asked to address and we will start with the first one, that second paragraph, in terms of guiding principles.

It would be helpful for me, and perhaps for others, is there a definition of or a standard or a legal definition of normal growth right now that the agency uses or is the science base for that the AAP report, '88 report that we received

that has a recommendation for weight gain or expected weight gain, or is it the CDC current standard or reference, NCHS.

DR. YETLEY: We don't have a formal definition, per se. We have relied on the CONAC report, '86 or whenever it was, and we have a proposed definition in the 1996 proposal, but we have not -- at this point, we don't have an official definition.

DR. GARZA: Can you remind us of what that proposed definition is?

DR. YETLEY: Basically, we were proposing that normal physical growth be assessed by the measures, usual weight and whatnot, and it be compared to -- the growth of infants on the test formula or the new formula be compared to the growth of infants on a control formula that had a history of use as an empirical formula, and then there is also a proposal that individual and group data be compared to national standards, also.

DR. STALLINGS: A follow-up to that. How do breast-fed, the growth of breast-fed infants,

exclusively breast-fed infants work into what might be the guidelines for growth?

DR. YETLEY: We haven't included a comparison to breast-fed infants in these proposals and they're not in the CONAC guidelines. I think at the next meeting, when we get into evaluations of growth, that's a legitimate question.

DR. STALLINGS: But it's currently not a part of the framework.

DR. GARZA: Are there others? Dr. Montville.

DR. MONTVILLE: I would just like to know if the limitation of the discussion to physical growth is the statutory. It strikes me that requiring a formula to keep an infant on the growth curve is not a very -- it doesn't appear rigorous in terms of total nutrition.

DR. GARZA: Beth or Chris?

DR. YETLEY: The statutory requirement is that FDA implement quality factors and it is up to the FDA to define what those quality factors are. I think that the CONAC report did say that physical

growth is a useful indicator.

I think part of what we are saying, also, is by opening up in the next two meetings, looking at more closely at how we measure physical growth and then, also, looking at the possibility of needing additional nutrients, we're asking the question in terms of getting the most sensitive and useful measures to evaluate quality factors.

The feeling was we needed to start with some general guiding principles so that that would guide that process, and then as you go through that process, you can also come back and see if your guiding principles are still as functional as you wanted or if you want to bring some revisions to them.

DR. GARZA: Are there other questions of Beth or Chris?

DR. BAKER: I have one other question. That is, are we looking strictly at the first year when infants will be taking formula or are we looking at growth beyond the first year, where there may be an effect from growth during the first

year?

DR. YETLEY: The infant formula, we propose to define it as for the first 12 months of life, and, clearly, the sole source and use of infant formulas, from a practical perspective, is the first four to six months. So you're worried about that.

I think there is a legitimate question, given evolving science, as to whether or not there needs to be some longer term evaluation and what should be that and what does it mean, and, again, I think those are issues that should come up at a subsequent meeting or can come up at a subsequent meeting.

DR. LEWIS-TAYLOR: Just so that we can clarify and that you do understand the charge to the committee, because I'm concerned that we clarify that. On page one, as you pointed out, the first two paragraphs are the first question and should be addressed over two or three meetings.

The third paragraph begins the specific questions for which we are asking closure by --

DR. GARZA: By tomorrow at noon. That's right.

DR. LEWIS-TAYLOR: Just to clarify.

DR. GARZA: Sure. Is that clear to everyone? Before we move on. Okay. We are scheduled to take a break at 10:00. We are there now. Let's try to get back -- we're a little bit ahead of schedule, but I anticipate that, in fact, we may need the added time for discussion.

We are scheduled to be back by 10:20. So let's try to be back at the table at 10:20. Those of you that have been at meetings that I've chaired will understand that we will be back at 10:20 and we will start at 10:20.

So let's get back and begin our more general discussion at that point. Thank you.

[Recess.]

DR. GARZA: I am going to ask that whoever handles the microphones to please be on time. My comment about getting started on time applies equally to you, because we can't get started until you're at your seat.

I apologize to those members of the committee that showed up at 10:20. The mics were off and we couldn't get started, because this needs to be recorded.

We're going to have -- Beth and Chris want to review the questions for today for the group, and then I've checked with the executive secretary and we do have the flexibility not to wait until 1:00, as was published in the Federal Register, for public comment, because, in fact, everyone who had registered is here.

So before we open it up for general discussion, it would be very useful to hear those comments. So that, in fact, your comments will reflect both what we heard from the government and what we will hear from the public.

So before we get started with public comments, let me ask either Chris or Beth then to go over those.

DR. LEWIS-TAYLOR: We just wanted to take a second, because there appeared to be some confusion. I guess we could go back to the first

slide again. There is, as we have articulated, we hope we have articulated, a general question which can be discussed preliminarily today and then we expect that you would take this question up in detail for the second and third meetings, and we will be glad to get this printed and pass it out, if it helps.

DR. GARZA: That would help, I think, if you could.

DR. LEWIS-TAYLOR: We will go ahead and have that done for you. So this general question is not what we're expecting you to come to closure on today and, in fact, we are allowing another two meetings, as appropriate, to discuss this and come up with closure on this set of questions or this question later on.

It's the next slide and one after that that today's questions really -- we see a question 1-A, B, and C, and I confess I don't have my glasses on, so I can't read it, but I'm hopeful that you folks can basically see that we're talking about generalizability and asking a question about

generalizability, one population to another, one product to another or combination of, and we have cited the example of pre-term to term and healthy to diseased.

So that is a specific question that we are hoping, before the close of this meeting, you folks will be able to address.

Then question two, on the next slide, today's question, it's relative to infant formula supporting normal growth between the test and control groups, which have clinical concerns. The study was not provided to detect. That's a specific question we're hoping closure for.

Then I believe there is a third question we're hoping closure on, on the differences in nutrition -- attrition rates. Some day I will bring my glasses. Attrition rates between the study groups.

So that first slide, over three sessions. We will get these printed off and make it clear that these are the ones we're hoping for closure by the end of tomorrow.

DR. GARZA: Good. And you'll get those to us by lunch time today, is that possible?

DR. LEWIS-TAYLOR: Sylvia is nodding yes.

DR. GARZA: Thank you, Sylvia. And are there questions from the group regarding the three questions that have now been posed by the FDA to us? Does that clarify, for those of you who had remaining questions, what the task for us is?

Okay. Good. Let's move on then to the public comment period. We have six individuals who will be addressing the committee. Each has been given approximately seven minutes. I will ask the executive secretary to keep time, to make sure that, in fact, each of you adheres to that, so that, in fact, we can get through the agenda as scheduled.

The first is Mr. Robert Gelardi, President of the International Formula Council.

MR. GELARDI: Thank you very much. On behalf of the entire U.S. formula industry, we appreciate the opportunity to address members of the FDA's Food Advisory Committee and the expert

panel on infant formula, regarding quality factors.

U.S. infant formula manufacturers are acutely aware of the importance of our products to infant nutrition and health. We recognize that infant formulas are often the sole source of nutrition for infants and that design, manufacture, and control of infant formula, therefore, requires special care.

Additionally, the industry fully acknowledges that breast feeding is the preferred feeding method for most babies, and manufacturers constantly work on improving their formulas to incorporate as much as possible the nutritional benefits provided by human milk.

Formulas on the market today are designed to meet or exceed nutritional standards recommended by the Committee on Nutrition of the American Academy of Pediatrics and mandated by the Infant Formula Act of 1980, as amended in 1986.

It is our responsibility as manufacturers to have the best application of science and assure any new or changed formulation will support normal

growth and meet required quality factors.

I would like to identify what we believe are the critical issues for consideration and then discuss them in greater detail.

First, the process by which the important issue of quality factors is addressed should be a thorough one, allowing sufficient time for the best input, so that the outcome is in the best interest of infants' health.

Second, clinical studies in infants should be scientifically, medically, and ethically justified. Third, when studies are needed and what they encompass should take into consideration the practical scientific knowledge best obtainable from the manufacturer, and, as appropriate, this knowledge may also include relevant international experience.

Fourth, any generalization of findings from a clinical study in one population to other populations in the absence of specific clinical data should be reviewed on a case by case basis for its scientific merit and relevance.

Fifth, the infant formula industry operates under a comprehensive pre-market notification process, unlike any other food in the United States, and based on the best interest of infants and sound science, the law requires pre-market notification and not pre-approval of new infant formulas.

With respect to the first point, we strongly recommend that any deliberations or determinations on quality factors for infant formula take the time necessary and offer the opportunity for the best scientific, medical, and practical input available, keeping in mind that the industry already has access to the best scientific, medical, and practical input, both internally and through academic consultants, and is already held fully responsible under the law for ensuring the quality of formulas.

The infant formula industry looks forward to providing additional comments and having the opportunity to actively participate in any deliberations affecting infant formula

requirements, since we are most intimately and most broadly equipped to address these issues.

For example, we have provided extensive comments to the Life Science Research Office regarding their review of nutrient requirements for both term and pre-term infants, to the American Academy of Pediatrics on clinical testing of new infant formulas, and on numerous FDA proposals.

Second, we are concerned about an apparent trend for FDA to require growth studies unsupported by scientific need. Such a practice does not consider all the relevant data and ignores FDA's own ethical guidelines issued as an interim rule in 2001 to provide additional safeguards for children enrolled in clinical studies involving FDA regulated products.

It is critical to distinguish between what is truly needed and can be provided by a growth or other clinical study and what may be primarily of academic interest.

It would be especially troubling of studies that were unnecessary, invasive, or

unreliable were deemed necessary because of an inappropriate assessment of what is required.

It is critical that FDA's ethical guidelines as to when it is appropriate to perform testing in infants be integrated into FDA decision-making so as not to subject infants to unwarranted testing. It also is important to recognize the practical difficulties involving and doing unnecessary research in infants. For example, the cost of the study, the delay in time to market, and the scarcity of subjects.

For guidance on this issue, including whether growth or other studies are needed, we recommend FDA be encouraged to rely more heavily upon those with pediatric nutrition experience who regularly conduct infant clinical studies, instead of relying on theoretical arguments for growth studies that are not based on sound practical scientific experience.

Third, while it is very important that FDA provide general guidance on when and what clinical studies may be needed, any regulations on the

actual conduct of growth or other studies should provide a framework and should not be overly prescriptive.

FDA earlier proposed the following two quality factors; namely, that infant formulas shall, one, support normal growth and, two, contain protein of sufficient quality to meet the protein requirements of infants.

Manufacturers thus currently establish that any new infant formula, including an existing formula to which a major change has been made, meets these required quality factors. It is important that any further clarification of quality factors for infant formula be science-based and if it is deemed necessary to have additional guidelines, they should be transparent and appropriate. Exemptions should be established.

Any requirements should be biologically informative and reasonably well standardized. Decisions on when growth studies are required should be based on the manufacturer's knowledge and experience on specific ingredient additions,

product manufacture, the level and reason for addition of the ingredient, and the anticipated outcome that could be expected from the conduct of such a trial.

When a clinical study is warranted, numerous criteria should be considered to make informed decisions on which type of study, growth, trial or other, is most appropriate. These decisions should consider the type of change, for example, whether it's major or minor, the clinical studies' scientific merit, strong ethical considerations, such as the invasive nature of the study and overall medical justification.

This also includes practical scientific knowledge best obtainable from the manufacturer. I would like to add an important point; namely, that industry currently follows the good clinical practice and this includes the elements contained in FDA's 1996 proposed rule.

We plan to provide you extensive information we believe will be helpful in addressing the tentative guiding principles that

we all just received, you and we.

MS. HAYDEN: You have about 30 more seconds.

MR. GELARDI: I would hope that I would have the time to finish, since I am speaking on behalf of the industry.

DR. GARZA: I'm sorry. We have time at the end of the session. To make sure everybody has an equivalent amount of time, we can ask you to come back, if we still have time at the end.

MR. GELARDI: Okay. Well, I will then have to conclude. I think it is important to recognize that the infant formula industry has been operating by law under notification process for over 20 years, with a remarkable record of providing safe and useful infant formulas. Manufacturers must notify FDA 90 days prior to marketing a new infant formula, of an existing infant formula which has a major change.

Under this process, infants have been well protected and the industry and the FDA should take great pride in the safety of infant formula. FDA's

infant formula review responsibility is not in a new pre-approval process. The Infant Formula Act of 1980 did not authorize any form of pre-clearance by the FDA on the marketing of an infant formula.

And I would say, get back to a couple of these other points, but I really believe that it is critical that we work together with the committee, with the --

DR. GARZA: I'm sorry. Your time is really up. Could you please conclude?

MR. GELARDI: With FDA. That's all I had in finishing.

DR. GARZA: Thank you. Dr. Susan Carlson, on the applicability of pre-term infant data to term infants.

DR. CARLSON: Thank you very much for allowing me to address you today. As Dr. Garza has said, my name is Susan Carlson. I'm a Professor of Pediatrics and Dietetics and Nutrition at the University of Kansas Medical Center.

My expertise in speaking to you today comes primarily from five clinical trials that I

conducted while a professor of pediatrics in OB/GYN at the University of Tennessee-Memphis between 1983 and 1997.

Those trials were supported, four of them, by Ross Laboratories, one by Meade Johnson. Three of the pre-term trials, four of them were pre-term -- three were pre-term trials, two were term, and the three pre-term trials were also supported by the National Institute of Child Health and Human Development.

I am here today as the paid consultant of Wyeth Laboratories. I have never done a study with Wyeth Laboratories.

Two of the clinical trials that we conducted in Memphis found lower growth, and I want to return to those at the very end of my comments, but, first, I wanted just to say a couple of things in a general way. We're asked today to speak to the question of when is it appropriate to generalize the results from the clinical studies done in one population to another population, whether the difference in those populations be

cultural, geographic, gender, age, physiologic, maturity, or et cetera.

Of course, as we are discussing infant formula, we are talking about that that is a complex matrix of nutrients or ingredients that supply nutrients that are essential for optimal growth and development of infants and when they are fed as a sole source of food.

The scientific community has very well understood rules for standards of generalizing data, which includes the need to do an intervention in a variety of populations to gain the greatest understanding of efficacy, as well as to uncover, if possible, any concerns about safety.

And, in fact, I would argue that this variety of conditions under which we do research actually strengthens the final conclusions and our confidence in moving forward.

If generalization were not permitted, which is kind of the logical, if we take it to that logical conclusion, there is a real risk of populations not receiving interventions that would

benefit them in a timely manner, and that is the perspective from which I am approaching you today.

Now, on the specific question of whether data generated in pre-term infants can be generalized to term infants or vice versa, and specifically considering growth, which seems to be the point of today, in large degree, I would say that the answer to that question depends.

Very low birth weight infants quadruple their weight between 28 weeks and two months corrected age, 28 weeks gestational age. Term infants triple their weight in the first 12 months of life. The pre-term infant is much more vulnerable to any kind of insult on growth and I would maintain that if you do not find an effect of an ingredient or a complex mixture of ingredients on growth of the pre-term infant, you have no reason to be concerned about feeding that ingredient in the same amount to term infants.

On the other hand, I would not conclude that in reverse, and, again, I'm talking about a specific ingredient.

And I wanted from here to go into about five slides, which will conclude my presentation to you. Alexander Lapalone and I, from the Children's Nutrition Research Center, last year, reviewed all of the studies that have published data on growth on infants who were fed one particular ingredient in infant formula, that's the long chain polyunsaturated fatty acids, docosahexaeonic acid, and/or docosahexaeonic acid and arachidonic acid.

There are a number of term and pre-term studies, and I want to just give you a little flavor of what I'm talking about using this specific ingredient.

So if you will kindly put those up. I have a great lady here to help me.

DR. GARZA: While we're awaiting the signal to arrive, do any of you have any questions to Dr. Carlson? All right. There they are.

DR. CARLSON: Okay. So I ask the question, what is the evidence that DHA reduces growth. I told you already that two of the studies that showed effects on growth were done by me at

the University of Tennessee. Thirteen published studies have measured growth in pre-term infants fed DHA or DHA and ARA. Of these, in only six was the diet fed for sufficient time, and I used some fairly loose standards here, at least four months, and the group size large enough, and I said there has to be an N of at least 25 per group.

We could argue this point because, in fact, I believe truly that you need at least 25 per group if you normalize the data, and many people do not normalize their data, which means they don't correct for gender effects, and this is very important pre-term infants.

So ideally you would have a group the size of 30 and that was what would be needed to have the power to detect an effect on growth.

Next slide, please. We'll just go quickly through these. I think you skipped one. Okay. Of the six studies that were, in my opinion, could be argued, had the power to detect an effect on growth, that is, to reject the null hypothesis, three fed DHA without ARA, two of those were mine,

and all three found lower growth either in the group as a whole or in males only.

Three fed DHA with ARA and none found lower growth, lower weight, length, or head circumference at any age. In fact, one found higher weight, length, and head circumference at zero, two and four months.

Next slide. Now, in the term studies, there have been 15 studies that have reported anthropometric data from term infants fed DHA or DHA and ARA and of these, in only seven do I think the diet was fed for sufficient time or to group sizes large enough to have the power to reject the null hypothesis.

Next slide. Of these seven studies that were designed with the power to accept or reject the null hypothesis, none found an effect of DHA on weight, length, or head circumference. Several also measured mid-arm circumference and various skin folds and found no effect on these measures either.

All seven studies included at least one

group that received DHA and ARA and three of these studies included one group that received only DHA, which speaks a bit to my point of it's possible to put an ingredient in that would not have an effect in the term infant, but could have an effect in the pre-term infant, and I believe that's on the next slide.

So what can we conclude from this? Pre-term, but not term infants, may have somewhat lower growth if they are fed formulas with DHA alone. Including ARA with DHA seems to prevent any adverse effects on growth of including DHA in formula in the pre-term infant.

Term infants fed formulas with DHA alone for as long as 12 months have not shown any lower growth than when fed ordinary formula or formula with DHA and ARA, and these are the matrices that are being added currently to term formula for the two companies that have been given permission to add them to infant formula.

Finally, one more slide. So the problem, as I see it, is given a formula with DHA fed to

pre-term infants, with the statistical power to reject the null hypothesis, and no effect on growth, then the question that we're asking, is there any reason to expect that growth would be affected if the same DHA or combination of DHA and ARA were fed to term infants.

I think this answer is so obviously no, that I didn't even put an answer on here.

Thank you very much for your attention.

DR. GARZA: Thank you. We have about 30 seconds for questions. Does anyone have a point of clarity for Dr. Carlson? Thank you.

The third individual is Dr. Michael Caplan, on issues of growth, also related to pre-term and term infants. Dr. Caplan?

DR. CAPLAN: Good morning. My name is Micky Caplan. I am the Chairman of the Department of Pediatrics and head of neonatology at Evanston Northwestern Health Care, and associate professor of pediatrics at Northwestern University Medical School.

I have engaged in research in the

pathogenesis of neonatal necrotizing enterocolitis for the last many years, but I am here today as a clinical neonatologist to speak to my experience as to the generalizability of studies done in premature babies to relate to term infants as one population to another.

Okay. Good. Let's move on then to the public comment period. We have six individuals who will be addressing the committee. Each has been given approximately seven minutes. I will ask the executive secretary to keep time, to make sure that, in fact, each of you adheres to that, so that, in fact, we can get through the agenda as scheduled.

The first is Mr. Robert Gelardi, President of the International Formula Council.

MR. GELARDI: Thank you very much. On behalf of the entire U.S. formula industry, we appreciate the opportunity to address members of the FDA's Food Advisory Committee and the expert panel on infant formula, regarding quality factors.

U.S. infant formula manufacturers are

acutely aware of the importance of our products to infant nutrition and health. We recognize that infant formulas are often the sole source of nutrition for infants and that design, manufacture, and control of infant formula, therefore, requires special care.

Additionally, the industry fully acknowledges that breast feeding is the preferred feeding method for most babies, and manufacturers constantly work on improving their formulas to incorporate as much as possible the nutritional benefits provided by human milk.

Formulas on the market today are designed to meet or exceed nutritional standards recommended by the Committee on Nutrition of the American Academy of Pediatrics and mandated by the Infant Formula Act of 1980, as amended in 1986.

It is our responsibility as manufacturers to have the best application of science and assure any new or changed formulation will support normal growth and meet required quality factors.

I would like to identify what we believe

are the critical issues for consideration and then discuss them in greater detail.

First, the process by which the important issue of quality factors is addressed should be a thorough one, allowing sufficient time for the best input, so that the outcome is in the best interest of infants' health.

Second, clinical studies in infants should be scientifically, medically, and ethically justified. Third, when studies are needed and what they encompass should take into consideration the practical scientific knowledge best obtainable from the manufacturer, and, as appropriate, this knowledge may also include relevant international experience.

Fourth, any generalization of findings from a clinical study in one population to other populations in the absence of specific clinical data should be reviewed on a case by case basis for its scientific merit and relevance.

Fifth, the infant formula industry operates under a comprehensive pre-market

notification process, unlike any other food in the United States, and based on the best interest of infants and sound science, the law requires pre-market notification and not pre-approval of new infant formulas.

With respect to the first point, we strongly recommend that any deliberations or determinations on quality factors for infant formula take the time necessary and offer the opportunity for the best scientific, medical, and practical input available, keeping in mind that the industry already has access to the best scientific, medical, and practical input, both internally and through academic consultants, and is already held fully responsible under the law for ensuring the quality of formulas.

The infant formula industry looks forward to providing additional comments and having the opportunity to actively participate in any deliberations affecting infant formula requirements, since we are most intimately and most broadly equipped to address these issues.

For example, we have provided extensive comments to the Life Science Research Office regarding their review of nutrient requirements for both term and pre-term infants, to the American Academy of Pediatrics on clinical testing of new infant formulas, and on numerous FDA proposals.

Second, we are concerned about an apparent trend for FDA to require growth studies unsupported by scientific need. Such a practice does not consider all the relevant data and ignores FDA's own ethical guidelines issued as an interim rule in 2001 to provide additional safeguards for children enrolled in clinical studies involving FDA regulated products.

It is critical to distinguish between what is truly needed and can be provided by a growth or other clinical study and what may be primarily of academic interest.

It would be especially troubling of studies that were unnecessary, invasive, or unreliable were deemed necessary because of an inappropriate assessment of what is required.

It is critical that FDA's ethical guidelines as to when it is appropriate to perform testing in infants be integrated into FDA decision-making so as not to subject infants to unwarranted testing. It also is important to recognize the practical difficulties involving and doing unnecessary research in infants. For example, the cost of the study, the delay in time to market, and the scarcity of subjects.

For guidance on this issue, including whether growth or other studies are needed, we recommend FDA be encouraged to rely more heavily upon those with pediatric nutrition experience who regularly conduct infant clinical studies, instead of relying on theoretical arguments for growth studies that are not based on sound practical scientific experience.

Third, while it is very important that FDA provide general guidance on when and what clinical studies may be needed, any regulations on the actual conduct of growth or other studies should provide a framework and should not be overly

prescriptive.

FDA earlier proposed the following two quality factors; namely, that infant formulas shall, one, support normal growth and, two, contain protein of sufficient quality to meet the protein requirements of infants.

Manufacturers thus currently establish that any new infant formula, including an existing formula to which a major change has been made, meets these required quality factors. It is important that any further clarification of quality factors for infant formula be science-based and if it is deemed necessary to have additional guidelines, they should be transparent and appropriate. Exemptions should be established.

Any requirements should be biologically informative and reasonably well standardized. Decisions on when growth studies are required should be based on the manufacturer's knowledge and experience on specific ingredient additions, product manufacture, the level and reason for addition of the ingredient, and the anticipated

outcome that could be expected from the conduct of such a trial.

When a clinical study is warranted, numerous criteria should be considered to make informed decisions on which type of study, growth, trial or other, is most appropriate. These decisions should consider the type of change, for example, whether it's major or minor, the clinical studies' scientific merit, strong ethical considerations, such as the invasive nature of the study and overall medical justification.

This also includes practical scientific knowledge best obtainable from the manufacturer. I would like to add an important point; namely, that industry currently follows the good clinical practice and this includes the elements contained in FDA's 1996 proposed rule.

We plan to provide you extensive information we believe will be helpful in addressing the tentative guiding principles that we all just received, you and we.

MS. HAYDEN: You have about 30 more

seconds.

MR. GELARDI: I would hope that I would have the time to finish, since I am speaking on behalf of the industry.

DR. GARZA: I'm sorry. We have time at the end of the session. To make sure everybody has an equivalent amount of time, we can ask you to come back, if we still have time at the end.

MR. GELARDI: Okay. Well, I will then have to conclude. I think it is important to recognize that the infant formula industry has been operating by law under notification process for over 20 years, with a remarkable record of providing safe and useful infant formulas. Manufacturers must notify FDA 90 days prior to marketing a new infant formula, of an existing infant formula which has a major change.

Under this process, infants have been well protected and the industry and the FDA should take great pride in the safety of infant formula. FDA's infant formula review responsibility is not in a new pre-approval process. The Infant Formula Act

of 1980 did not authorize any form of pre-clearance by the FDA on the marketing of an infant formula.

And I would say, get back to a couple of these other points, but I really believe that it is critical that we work together with the committee, with the --

DR. GARZA: I'm sorry. Your time is really up. Could you please conclude?

MR. GELARDI: With FDA. That's all I had in finishing.

DR. GARZA: Thank you. Dr. Susan Carlson, on the applicability of pre-term infant data to term infants.

DR. CARLSON: Thank you very much for allowing me to address you today. As Dr. Garza has said, my name is Susan Carlson. I'm a Professor of Pediatrics and Dietetics and Nutrition at the University of Kansas Medical Center.

My expertise in speaking to you today comes primarily from five clinical trials that I conducted while a professor of pediatrics in OB/GYN at the University of Tennessee-Memphis between 1983

and 1997.

Those trials were supported, four of them, by Ross Laboratories, one by Meade Johnson. Three of the pre-term trials, four of them were pre-term -- three were pre-term trials, two were term, and the three pre-term trials were also supported by the National Institute of Child Health and Human Development.

I am here today as the paid consultant of Wyeth Laboratories. I have never done a study with Wyeth Laboratories.

Two of the clinical trials that we conducted in Memphis found lower growth, and I want to return to those at the very end of my comments, but, first, I wanted just to say a couple of things in a general way. We're asked today to speak to the question of when is it appropriate to generalize the results from the clinical studies done in one population to another population, whether the difference in those populations be cultural, geographic, gender, age, physiologic, maturity, or et cetera.

Of course, as we are discussing infant formula, we are talking about that that is a complex matrix of nutrients or ingredients that supply nutrients that are essential for optimal growth and development of infants and when they are fed as a sole source of food.

The scientific community has very well understood rules for standards of generalizing data, which includes the need to do an intervention in a variety of populations to gain the greatest understanding of efficacy, as well as to uncover, if possible, any concerns about safety.

And, in fact, I would argue that this variety of conditions under which we do research actually strengthens the final conclusions and our confidence in moving forward.

If generalization were not permitted, which is kind of the logical, if we take it to that logical conclusion, there is a real risk of populations not receiving interventions that would benefit them in a timely manner, and that is the perspective from which I am approaching you today.

Now, on the specific question of whether data generated in pre-term infants can be generalized to term infants or vice versa, and specifically considering growth, which seems to be the point of today, in large degree, I would say that the answer to that question depends.

Very low birth weight infants quadruple their weight between 28 weeks and two months corrected age, 28 weeks gestational age. Term infants triple their weight in the first 12 months of life. The pre-term infant is much more vulnerable to any kind of insult on growth and I would maintain that if you do not find an effect of an ingredient or a complex mixture of ingredients on growth of the pre-term infant, you have no reason to be concerned about feeding that ingredient in the same amount to term infants.

On the other hand, I would not conclude that in reverse, and, again, I'm talking about a specific ingredient.

And I wanted from here to go into about five slides, which will conclude my presentation to

you. Alexander Lapalone and I, from the Children's Nutrition Research Center, last year, reviewed all of the studies that have published data on growth on infants who were fed one particular ingredient in infant formula, that's the long chain polyunsaturated fatty acids, docosahexaeonic acid, and/or docosahexaeonic acid and arachidonic acid.

There are a number of term and pre-term studies, and I want to just give you a little flavor of what I'm talking about using this specific ingredient.

So if you will kindly put those up. I have a great lady here to help me.

DR. GARZA: While we're awaiting the signal to arrive, do any of you have any questions to Dr. Carlson? All right. There they are.

DR. CARLSON: Okay. So I ask the question, what is the evidence that DHA reduces growth. I told you already that two of the studies that showed effects on growth were done by me at the University of Tennessee. Thirteen published studies have measured growth in pre-term infants

fed DHA or DHA and ARA. Of these, in only six was the diet fed for sufficient time, and I used some fairly loose standards here, at least four months, and the group size large enough, and I said there has to be an N of at least 25 per group.

We could argue this point because, in fact, I believe truly that you need at least 25 per group if you normalize the data, and many people do not normalize their data, which means they don't correct for gender effects, and this is very important pre-term infants.

So ideally you would have a group the size of 30 and that was what would be needed to have the power to detect an effect on growth.

Next slide, please. We'll just go quickly through these. I think you skipped one. Okay. Of the six studies that were, in my opinion, could be argued, had the power to detect an effect on growth, that is, to reject the null hypothesis, three fed DHA without ARA, two of those were mine, and all three found lower growth either in the group as a whole or in males only.

Three fed DHA with ARA and none found lower growth, lower weight, length, or head circumference at any age. In fact, one found higher weight, length, and head circumference at zero, two and four months.

Next slide. Now, in the term studies, there have been 15 studies that have reported anthropometric data from term infants fed DHA or DHA and ARA and of these, in only seven do I think the diet was fed for sufficient time or to group sizes large enough to have the power to reject the null hypothesis.

Next slide. Of these seven studies that were designed with the power to accept or reject the null hypothesis, none found an effect of DHA on weight, length, or head circumference. Several also measured mid-arm circumference and various skin folds and found no effect on these measures either.

All seven studies included at least one group that received DHA and ARA and three of these studies included one group that received only DHA,

which speaks a bit to my point of it's possible to put an ingredient in that would not have an effect in the term infant, but could have an effect in the pre-term infant, and I believe that's on the next slide.

So what can we conclude from this? Pre-term, but not term infants, may have somewhat lower growth if they are fed formulas with DHA alone. Including ARA with DHA seems to prevent any adverse effects on growth of including DHA in formula in the pre-term infant.

Term infants fed formulas with DHA alone for as long as 12 months have not shown any lower growth than when fed ordinary formula or formula with DHA and ARA, and these are the matrices that are being added currently to term formula for the two companies that have been given permission to add them to infant formula.

Finally, one more slide. So the problem, as I see it, is given a formula with DHA fed to pre-term infants, with the statistical power to reject the null hypothesis, and no effect on

growth, then the question that we're asking, is there any reason to expect that growth would be affected if the same DHA or combination of DHA and ARA were fed to term infants.

I think this answer is so obviously no, that I didn't even put an answer on here.

Thank you very much for your attention.

DR. GARZA: Thank you. We have about 30 seconds for questions. Does anyone have a point of clarity for Dr. Carlson? Thank you.

The third individual is Dr. Michael Caplan, on issues of growth, also related to pre-term and term infants. Dr. Caplan?

DR. CAPLAN: I only have a few points to make, and one is that the premature baby is really a continuum. In our clinical practice, prematurity has changed over the years. Now, while we take care of 23-week and 24-week premature babies, it's quite a different patient than the premature babies who are at 33 and 34 weeks gestation.

Those babies, at that gestational age, in fact, go to normal newborn nursery and are

discharged at that age. We look at those 34, 33-week babies, as many of you on the committee know, really as close to term infants and they go home often from our nursery exclusively on breast feeding, and grow well and do exceptionally well.

And so I think it's really important, from my perspective, to understand the continuum so that a study done on premature babies at 24 or 26 weeks is a very different study than one done on premature babies at 33, 34 weeks and above.

As an aside, I would like to just give my bias that I think that the FDA should consider standardizing feeding studies to breast fed infants and not control formula, because I think that those growth curves might be a little different and I think that we should use the gold standard as breast feeding, but I'm not hearing support of the Infant Formula Council, per se.

What I would also then like to say is that the physiology of gastrointestinal functions of the premature baby clearly are different than in full term babies, based on many studies done over the

years.

However, again, those differences are on a continuum. We know that the absorptive function, the digestive functions, metabolism of certain nutrients, the differences in gastric acid secretion, intestinal motility, there are many differences in the premature baby compared to the term infant, just like there is in host defense, which might be an important factor in necrotizing enterocolitis.

Nonetheless, many of these functions approach term levels in babies at 31, 32, 33 weeks gestation. For example, fat absorption, protein digestion had been shown to be almost identical in 32-week premature babies than they are in term infants.

So it's important, again, to remember the continuum with respect to pre-term babies and term infants.

I'd like to echo what Dr. Carlson said. To my mind, a premature baby who is born at the 30 or so weeks and is in the study for four months is

then tripled or quadrupled their birth weight. We will pick up on the sensitivity differences in growth just as if we looked at a term infant and watched them grow for one year.

I think that's an important point in giving us confidence in safety of a feeding regimen looking at growth in that context.

Finally, I guess, in conclusion, my perspective is then that although I would not be comfortable, as a clinical academic neonatologist, in generalizing a term baby's feeding study to a premature baby, I would be quite, quite comfortable in generalizing then the premature results of growth on then a term infant.

Obviously, that's not the same as to whether there would be a beneficial outcome in some other factor, but certainly on safety, with respect to adverse events and growth, that would give me great comfort.

Thank you for your time, and I'd be happy to answer questions.

DR. GARZA: Thank you, Dr. Caplan. Are

there any questions?

DR. STALLINGS: Just a point of clarification. You are here on your own behalf or are you a consultant related to this work?

DR. CAPLAN: I'm sorry. I didn't clarify. I am here as a consultant, invited by Wyeth, but I don't have any other relationship with Wyeth in terms of investment or study.

DR. STALLINGS: Thank you.

DR. GARZA: Thank you, Dr. Caplan. Dr. Dwyer?

DR. DWYER: I wondered if you could give us any examples that go the other way; in other words, where a term infant might, in fact, be more sensitive than a pre-term infant? Are there any examples, allergy, anything?

DR. CAPLAN: Well, I really can't think of an example where a term infant would be more at risk for any particular problem than would be a premature infant. I mean, when we look at all the adverse events, they are significantly higher in our premature population than in our term infants,

and I really can't identify, in my mind, a specific situation where it would go the opposite way.

DR. GARZA: Dr. Caplan, one possibility that comes to my mind is Vitamin A, that, in fact, one may be able to come up with a rationale for increasing the level of Vitamin in a pre-term formula, given the accretion of Vitamin A in the last trimester.

Might this be a risk or do you feel that, in fact, the levels that one would be feeding to a pre-term infant that would be medically indicated to boost their Vitamin A stores could be sustained and determined for the first six months?

DR. CAPLAN: I don't think I answered to the fact that premature infants wouldn't need increased components of their formula. That's not what I tried to answer. But yes, there are certain things. I do believe the premature formulas do require certain additives in different concentrations, without a doubt.

I think that the question then is would the full-term infant tolerate those additives. I

really haven't spoken to that issue, although with the levels that are added to pre-term infants, I'm not convinced that there would be any dangers to the full-term infants if they received those quantities that are in the premature formula.

DR. GARZA: And I think that was the genesis of Dr. Dwyer's question. Thank you. Any other questions?

Dr. Eric Lien, also on the applicability of pre-term infant data to term infants.

DR. LIEN: While my presentation is coming up on the slide, I would just indicate that I provided you with a copy of the presentation. Due to time constraints, I will move through several examples extremely rapidly. If you are interested in more information, it is in hard copy in front of you.

Again, while I'm waiting for the slides to come up, I'm Eric Lien, Vice President of Nutritional Research and Development for Wyeth Nutrition. And, again, while we're waiting for the slides, just to indicate that Wyeth is the

manufacturer of infant formula, with over 80 years of experience. And our intent here is, of course, to provide quality infant formula products and we are driven by safety in this consideration.

The next slide, then, to start my presentation. The topic under consideration in front of the committee is the generalization of pre-term data to term infants, and that's exactly the topic I would like to comment on today.

Next slide. I will actually state three very basic principles, but these should be clear to everyone. It is our feeling that data related to the effects of a new ingredient should be fully considered, and that's all data. Data from well controlled trials done by GCP guidelines in pre-term infants are scientifically meaningful and relevant to the question and the findings from these well controlled trials may be generalized to term infants as part of a larger body of safety and efficacy data.

Next slide. I will actually give you several examples of the applicability of those data