TRANSCRIPT OF PROCEEDINGS

FOOD AND DRUG ADMINISTRATION

FOOD ADVISORY COMMITTEE

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COMMITTEE MEETING

ON INFANT FORMULA

Greenbelt, Maryland

April 5, 2002

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ON INFANT FORMULA

Friday, April 5, 2002

8:33 a.m.

Greenbelt Marriott
6400 Ivy Lane
Greenbelt, Maryland

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P R O C E E D I N G S

DR. GARZA: If everyone would take their seats, we're going to begin this morning with Dr. Beth Yetley and Chris Taylor will give us a bit of a recap based on their presentations, in trying to clarify some issues for the committee, with the hope then that whatever advice we might be able to provide at the end of the meeting would be then more information. And so we're going to take a few minutes, perhaps 15, to have them provide some clarification, and then we will return to those three questions.

At the present time, we'll see how the discussion unfolds. I am hoping that we will be finished before 12:00, so we may or may not take a break. We'll see how the discussion goes and then make our decision at that point. You can slip out quietly on your own, and we will register your opinions.

[Laughter.]

DR. GARZA: We tried locking the doors but I was told that was against fire regulations.

Okay, so let's begin. I don't know whether it will be Dr. Taylor or Dr. Yetley. Dr. Taylor? All right.

DR. TAYLOR: Good morning, and thank you very much for the opportunity just to do a brief recap. From yesterday's discussions, to no surprise, somehow the way the statute and the provisions work is at times less than clear, so we though we would try once again specifically responding in terms of some of the questions we heard raised yesterday.

I'm going to go back in the second slide here to this idea of the regulatory boxes. We presented a form of this slide yesterday, and based on the discussions, we've added just a few concepts. And it's a schematic, and the idea that there is a series of components, regulatory boxes, for infant formula.

And at the very top here, at the very top here you have the starting point of the safety of the ingredients for intended use. It happens to be regulated by Sections 409 and 201, which is why you

here us use those phrases all the time.

But it's important to recognize that this has been the classic safety issue. It happens to all foods and all food components, and it is ingredient specific. It's not relative to the product but it's for the ingredient. And if we follow your Echinacea example through, the one that was raised yesterday, Echinacea would start here as safety of an ingredient for intended use, in this case being infant formula.

We recognize that as these types of ingredients, the ingredients that are of interest in the addition to infant formula, change over time, some of them potentially physiologically active. But there are some issues here that need to be addressed, and some of you may be aware that recently we contracted with the National Academy of Sciences Institute of Medicine to explore methods for evaluating the safety of new or novel ingredients when intended for infant formula.

So this issue is not on the Advisory Committee's plate. It is being handled by the

Academy, and it's the classic issue of the safety of the ingredients for intended use.

From this point, this threshold point of the safety of the ingredient, you move to formulation and formulating the product. What we have in place under so-called Section 412 is a statutory check on the formulated product.

It's assurances for the specific product, and there are a variety of components that come into play, so called tabled nutrients, required nutrients, those things that are to be in infant formulas, the listed nutrients. There is the series of GMP issues and quality control issues, how it's processed, how you analyze for the ingredients, the nutrients in there.

Those two are part of a whole set of issues that go into providing assurances, as is the issue of quality factors. And it's highlighted here in red because the issue of quality factors is what we're putting on the Advisory Committee's plate.

Quality factors we will talk about again,

just to revisit in a second, but I noticed yesterday a lot of terms of efficacy and safety came up, and I think one way to think of quality factor is that it's a question of whether the specific product is still providing the required nutrients. It's a check on that, and in that case there does come into play phrases such as efficacy and safety, but it's efficacy and safety regarding the ability of the required nutrients to perform in that specific formulation.

So this is really what this Advisory Committee is all about. Once all of this happens and marketing occurs, it is possible to bring into play the concept of claims, and I think yesterday perhaps the question of efficacy for claims was put on the table.

The issue of truthful and not misleading is where this comes into play, Section 403(a). It's a post-marketing issue. The manufacturer is responsible for determining the substantiation upon which they decide to make this claim, and any activities on the part of the agency are post-

marketing.

But this is perhaps the classic efficacy questions that you folks were putting on the table yesterday. They come here post-marketing. Quality factors are a different set of issues, and while efficacy and safety sometimes come into play conceptually, again it's about the ability of that particular formulation to provide the require nutrients.

So once again going back to that red box, quality factors, we said that the assurances for final product were the first two we talked about, and then the quality factors. Is this specific product still providing nutrients in a biologically optimal way? The questions of interference, interaction, bioavailability, are what this Advisory Committee is being asked to address in a somewhat limited way.

Again, you can think of quality factors as being nutrient specific, bioavailability, and then the formulation as the totality. At this point what we're dealing with is normal physical growth.

As we heard yesterday, other things could be added over time as science evolved but, next slide, what we're about here is normal physical growth.

As part of this, then, the quality factor component, the issue of what is a major change came up yesterday, and to provide just a little bit of clarification, generally speaking a major change can fall into one of three categories: new manufacturer, a major change in processing, or a major change in formulation. That brings into play the concept of quality factors.

Some examples of this, new manufacturer to the U.S. market; introduction of a new form, for example, a powdered form of something that had been marketed previously as a liquid form; significant revision, addition, or substitution of macronutrient without prior experience relative to that ingredient; new processing in the line or in the plant, that constitutes a major change. And then what we are increasingly seeing is the use of a new or a novel constituent not required by the act.

Now, following up on that, again reemphasizing that quality factors are product specific, not ingredient specific, and that they have the potential to provide, to impact, to result in a total dietary change, one example is a new oil source. That often can be viewed as a major change, especially given the vulnerable population and the fact that it's a sole source issue.

With a new oil source, you would get a change in fatty acid composition. You would change the levels and the ratios of the saturated fat, the polys, the monos, the Omega-3's to the Omega-6. Given a target population such as this, the major change would be something that would invoke quality factors. There is a change also, obviously, in potential for interactions with other constituents.

So this is the kind of thing we're talking about when we talk about the questions we're putting in front of you, as far as how should we review these kinds of changes. What is the real bottom line here as far as how quality factors operate, is it's not a matter of experimenting to

see how a formula can be improved. That's not the congressional intent of quality factors, but rather quality factors are all about providing assurances for a marketed formula, and it's all about prior to marketing.

In the next slide we bring home, I think, again another clarification relative to yesterday's discussions. The whole point of a study is to show that there is no adverse effect on physical growth, given the current paradigm we're operating under, normal physical growth.

The way the process has operated the way we view it at FDA is that the end point runs along the route of bioequivalence, so that you're seeing similar growth. It's the proverbial two-tailed test, and in a moment I'll ask Beth Yetley, who has spent a great deal of time working in this area, to clarify for you this concept.

Where I think it's traditional to think but it's not necessarily the way the agency operates, certainly there is room for that, is that the end point of the studies does not run

necessarily down the beneficial route. It has not been historically growth more like breast-fed infants, which are a one-tailed test. We have been operating in this upper domain of bioequivalence, and I think much of your discussion was looking at the lower domain of the beneficial component.

Beth, I know you have done some work, and in fact some of this is based on what you have seen, if there is something you would like to add as far as clarifying the purpose of this for infant formula reviews.

DR. YETLEY: Well, I don't have too much to offer. I think that these concepts are something that you need to bring back when you talk about physical growth next time, because it really gets to the issue of whether we have operationalized it correctly and whether or not we have an appropriate interpretation. But I thought that part of the conversation yesterday was wanting to go to the beneficial arrow, and I'm not sure that we can quite go that far, although equivalence or support of adequate physical growth perhaps

could be operationalized differently.

Part of the confusion I think comes over the--because of the history of this. If you look at the COMA guidelines from '86 or '88, they really assumed bioequivalence to a comparable formula, and their criteria was a one-tailed test, that growth is either equal to or greater than, but the adverse effect was a lesser rate of growth. And I think what science is saying and what I was hearing yesterday is that that's not necessarily a valid interpretation. I think what FDA has done in recent years is to say a two-tailed test is more appropriate, that adversity could be either greater, significantly greater weight gain or significantly less weight gain.

I think one of the issues that came up yesterday, and the issue that we need to look at more closely at the next meeting, is whether or not it should be a one-tailed test and the tail should be in the direction of being more like breast milk. But I think those are issues for the future, but I thought that perhaps there needed to be some

clarification, that the purpose of the quality factor study is not to find new and improved mousetrap, new and improved formula, but to assure that to the best of our ability it is supporting normal physical growth.

DR. TAYLOR: Just for clarification, Beth is our lead scientist in nutrition, and I have served as office director, so you do see a kind of tag-team thing where her science informs our regulatory decisions, so she is an excellent source as far as clarifying some of the scientific parameters here.

So in terms of just going back to the goals and the purpose, Sylvia, if I could have the next slide, please, where we had hoped the Advisory Committee or how we hoped the Advisory Committee would structure itself, was that we saw you yesterday begin your discussion, your general--your responses to the general question.

And as we indicated, we're hopeful that the Ad Hoc Working Group will complete these discussions in two subsequent sessions. As we have

mentioned, we will be contacting the Ad Hoc Working Group to get together with dates. Anyone who is a member of the Food Advisory Committee, who would like to take part in that, you are certainly welcome. And these are public meetings, and we will try to get those organized in the near future, as soon as possible.

But as far as this meeting for April 4 and 5, we were asking you folks to come to closure on three specific questions by today. We did print those out and circulate them. On the next slide, the general question that you began to kind of noodle on yesterday, and that will be followed up in the future, was the one on your handout about what constitutes an appropriate and complete general science-based set of guiding principles.

And relative to this, if I could have the next slide, relative to this general question, we will use the discussion that we heard yesterday, and to the extent it happens today, to create a straw man for the Ad Hoc Group for future discussions about quality factors, specifically

normal physical growth. So we will try to make use of your discussions to create a better straw man for your next two meetings. We would also ask you what materials would the Ad Hoc Task Force like FDA to provide in terms of background, so that we will pull together for you, for your next meeting.

And then the next slide, as far as the specific questions for today, there were basically three, depending on how you count, three or five. One, generalizability relative to population and to product, and then the second about adverse events, and the third about attrition rates. And again, these were written and handed out yesterday.

If I could have the next slide, in terms of what we need, what would be useful, because that did come up yesterday, as far as the generalizability question, FDA would need a rationale for the responses that the committee members would provide us, and if the responses--it depends, and we put that in there because that seems to be the way the discussion was going--FDA would need criteria for when it's yes and criteria

for when it's no and a rationale for that. That's what would be most useful to us.

mpd And then in terms of the second and third question--next slide--adverse events, again, FDA would need advice and a rationale for that advice, and then the attrition rate, we'd need the advice and the rationale.

So I think that's it for the slides. We hope this was helpful.

If I could have the last slide, several of you yesterday requested that we provide hard copies of the slides on the comparison of the preterm and the term infants, and Sylvia, if you can just flip through those very quickly, we did a slide on the adequate intake, meaning breast milk, versus the Code of Federal Regulations formula for a couple of nutrients.

The next slide--again, these are in your handout and it I know it was the numbers you wanted--the referenced daily intakes.

Next slide, on the composition of marketed formulas, a comparison of preterm to term. Again,

this is in your handout.

Next slide, daily intakes for marketed formulas, preterm versus term, again in your handout, and then daily intakes for KG body weight, again, in your handout.

Several of you had asked for those as hard copies, so we've provided them as an attachment. Thank you very much.

DR. GARZA: Thank you. Are there any questions or comments?

[No response.]

DR. GARZA: If not, let's go back, then, and take up the three questions, beginning with the generalizability. I'd like to ask the group if there are any specific points of discussion that anyone would like to raise based on yesterday's exchanges that would help each of us clarify what our individual responses may be when we start going around the table.

The plan is that at the end of this general discussion, I will first ask the non-voting members of the group to give us responses with

rationales on all three questions, and then after they have done that--and I will do that in alphabetical order--then we'll go to the ad hoc group and then go at the end to members of the Food Advisory Committee, the permanent members.

But before we get to that part of the agenda, I want to make sure that, in fact, we each have an opportunity either to raise questions or make comments on all three questions. So I begin with question one.

[No response.]

DR. GARZA: All right. Maybe we'll be out of here by nine. I hope we get more.

What about question two? Any additional comments or concerns on the second question? All right, go ahead.

DR. BAKER: It seems like what the FDA is asking both in this question and in the first question is to have some written down rule for how to proceed, and I think that may be very difficult. In this question, though, we did bring up the possibility of an advisory, or an independent board

to review adverse events. Would that satisfy the FDA as a way of going about things, if you had a board that then would review adverse events and report their review to the FDA for a final decision?

DR. GARZA: I can't--

DR. BAKER: Would that satisfy that or not?

DR. GARZA: I can't speak for FDA. I will not--

DR. BAKER: Well--

DR. GARZA: My sense is--

DR. BAKER: Dr. Yetley, would that?

DR. YETLEY: I have to apologize. Chris and I were trying to figure something else out. Can you repeat your question as exactly as possible?

DR. BAKER: It appears to me that the FDA is looking for sort of solid written down guidelines for how to operate in the situation where adverse events are reported, and yesterday we did talk about having an independent review board

which would review adverse events and then report to the FDA. Would that satisfy the FDA as an operating mode or would they need more specific things than that? I think it would still be up to someone to decide what action needed to be taken about those adverse events, none, more review, or accept the report.

So there would still be a decision making thing that would be up to the FDA, but it would give them guidelines and evidence and support to make their decision. So would that satisfy the criteria or not? I mean--

DR. GARZA: Before Beth answers, as chair, I want to make sure that each committee member understands that as a committee member, you are free to tell the government whatever you wish, whether it satisfies FDA or not.

[Laughter.]

DR. GARZA: Our role here is not to bring joy to government officials--

[Laughter.]

DR. GARZA: --but to give them the best

advice you have, no matter how uncomfortable that advice may be. So I want to make sure that that's clearly understood before Beth answers because that's not--we can say, is that sufficient detail, which is a different question than would you find that answer satisfactory. Whether Beth finds it satisfactory or not--I'm sorry, Doctor--is irrelevant. So with that caveat, I want to make sure the groups understands that, all right, otherwise, our independence would be called into question and I certainly wouldn't want that to happen.

DR. YETLEY: I appreciate your comments, Bert.

[Laughter.]

DR. YETLEY: The question that we're concerned about is if the data that we have available to us has a significant difference in adverse--clinically significant adverse event reports between test and control, what do we do? How do we use that data? That is different than what should be done if those adverse events occur,

and I think that gets into study ethics issues and what not.

What would be useful for us is that if we are faced with a situation where one of the major pieces of evidence before us is a study that has large differences in adverse events between test and control, how or should we be using those data, and if you would feel that having an independent review to see if they can attribute those adverse events to the formula, or if they're unrelated to the formula, would inform us and make it--you could then provide some criteria as to whether or not those data would then be useful. I don't know if I'm making sense, but it's what would or should be done to make the data useful or are the data not useful.

DR. GARZA: So you're talking after the fact. You're evaluating a study that has adverse events and want to know--

DR. YETLEY: Right.

DR. GARZA: --because of the adverse events, does that negate the usefulness of the

study.

DR. YETLEY: Can that be used to evaluate whether or not that formula will support normal physical growth. That does not mean that the ethical issues should not be dealt with, but those would be dealt with, I think, in a different manner. But that's not to say those are not serious issues and don't need attention also.

DR. GARZA: Up here?

DR. GIACOIA: Yes, a point of clarification.

DR. GARZA: Would you identify yourself?

DR. GIACOIA: George Giacoia. Are you using the same classification of adverse events as it is used in drugs, measure versus reporting?

DR. YETLEY: Generally, the concept is clinically significant in the context of the infant population that we're dealing with.

DR. GIACOIA: Is it well defined? Does it need to be clarified for nutritional versus--

DR. YETLEY: It probably could stand some clarification, yes.

DR. GARZA: Other questions regarding either questions one or two? Dr. Dwyer?

DR. DWYER: I don't know if there's anything we can do about this right now, but I'm still uncertain as to exactly what is required and what is usually provided even if it's not required in existing studies that are being done now.

DR. GARZA: Can you provide a brief summary, either Beth or Chris? The question as I understand it is what are companies currently required to submit for the assurance factor or quality factors, along the--

DR. DWYER: What safeguards there are--

DR. GARZA: But for assurances and under quality factors specifically, rather than getting into the other two, and what is normally submitted above and beyond what is required.

DR. TAYLOR: We'll try the tag team approach on this, as well. There are not in place specific check lists for what is submitted. It's a package that the manufacturer creates to provide assurances. And so, assumedly, the manufacturer

for clinical trials would follow appropriate clinical trial procedures that, as I understand it, are standardized with IRBs or whatever.

And so the question of how the manufacturer handles adverse events is not one that we specifically provide as a set of check list items, if that's your question. And consequently, I think there's probably a range of what happens. Beth?

DR. YETLEY: Well, any of these studies that are done in support of a product that's to be regulated by FDA would come under both DHHS and FDA rules for protection of human subjects, clinical study guidelines, and what not. As Chris has indicated, we don't have specific requirements for X-number of studies of X-type. What we have historically relied upon and have been used were the comment guidelines for a clinical study to show that the new formula supports healthy growth, normal physical growth, and that is basically what we've proposed also, although that rule has not yet been finalized.

DR. GARZA: Do you want to follow up on that?

DR. HEUBI: Can I ask you a question? Jim Heubi. If you say they comply with DHHS standards, does that mean that all these studies require appropriate ethnicity and gender composition for acceptance?

DR. YETLEY: I can't give you all of the specifics on it, but any of the human subjects protection issues that are covered, and then there are some specific--it primarily comes under human subjects protection issues. Maybe we should get back to you on the more specific details for the next meeting.

DR. HEUBI: So, I guess, is diversity required for these studies? I guess that's the question, because--

DR. YETLEY: Yes, I can't--I don't know the answer right now.

DR. HEUBI: Because for NIH, all of us who submit applications now for any kind of clinical trial, we have to have composition that mirrors the

U.S. ethnic population and gender distribution.

DR. YETLEY: Well, the criteria is for the intended population, intended use population. The specifics on some of those details, I just don't know. We can find out and have them for the next meeting.

DR. GARZA: Is it my understand--I'm sorry, is there another question over here? It's my understanding that what is generally submitted, from your response, are growth data and supporting biochemical clinical sort of screens that are generally done on patients, I mean, that you may get serum proteins and electrolytes and cell counts of one sort or another, or is the general type of information that you see only the growth data with a report of adverse events and those adverse events being then defined by the PI and what he or she may decide to submit?

DR. YETLEY: I may ask for help from some of the staff, but the packages vary considerably. Some have biochemistries in addition to the growth data. I'm not sure that all do. No, all do not.

So it's very variable other than the growth data.

DR. GARZA: Okay. Dr. Dwyer, does that answer the--

DR. DWYER: Yes.

DR. HEUBI: Let me ask you a question. So the DHA data that was submitted to the FDA included growth data and biochemical results?

DR. YETLEY: I need to turn to Sue Ann.

DR. HEUBI: Sorry. I'm asking too specific of questions.

DR. YETLEY: Okay. She says it varied from manufacturer to manufacturer.

DR. HEUBI: Okay. Thank you.

DR. GARZA: Yes, Dr. Busta?

DR. BUSTA: We originally received a Food Advisory Committee Meeting on Infant Formula Charges and Questions, and in that was a tentative guiding principles for clinical studies. Whose is that?

DR. TAYLOR: That was the one that we put forward for possible discussion that you went through yesterday.

DR. GARZA: Those were just the sort of strong recommendations that were primarily drawn from the AEP report and the COMA report, but they were only intended to initiate discussion by the committee. They have no other standing as far as I know.

Now, in the end, we will be asked to make, in the general principle part of this discussion, that first question, we will be asked to address both the science base and the clinical base, which will then, I think, lead to our discussing both the design and the conduct of studies. Those discussions clearly got started with the hour and a half we had yesterday.

DR. BUSTA: Right. We concentrated on the COMA.

DR. GARZA: That's right, and the only reason for doing that was because that was the updated report, and as I think it was Dr. Thureen who suggested that, in fact, many of those recommendations appear to have come from the earlier AEP report and updated to a certain degree.

But that was only for getting discussions going. That has no other bearing and we could end up with a very different list, a partially different list. I doubt if we will agree, based on the discussion, totally with the COMA report.

DR. BUSTA: Thank you.

DR. GARZA: Yes?

DR. CLEMENS: Rog Clemens. You referred to Johanna's comment a moment ago. The American Academy of Pediatrics provided some basic guidelines in the 1980 report.

DR. GARZA: In the '88 report or 1980?

DR. CLEMENS: Actually, '88 report. Thank you very much, Bert. The manufacturers follow those basic guidelines and they particularly provide body weights and they provide recumbent lengths and they also provide head circumference types of data in addition to those interval data. They also provide the necessary biochemistries as deemed appropriate for that particular trial, and then they also provide additional data as, again, appropriate for the hypothesis. I hope that helps.

DR. GARZA: But it's important, the appropriateness is not determined by government or an independent agency. It is a decision of whoever's carrying out the investigation together with the sponsor.

DR. CLEMENS: The appropriateness is established by the investigators and the expert panels, developed by the various manufacturers, the manufacturers themselves.

DR. GARZA: Any other--?

[No response.]

DR. GARZA: All right. Then let's move on to question three. This has to do with attrition, the one that spent the least time yesterday.

[No response.]

DR. GARZA: Okay. Then let's begin going around the room. I will--at least from my perspective, it's very clear that responses to these three questions are going to be somewhat difficult because of the abstractness of the questions. I don't expect that each of you as you answer will be able to cover in sufficient detail

to provide guidance on every conceivable situation or condition that, in fact, the FDA may face regarding any of these three questions.

Having said that, try to provide as much guidance as you can, so that a simple yes or a simple no at times may be appropriate, and that would mean exactly what those words mean, no. So that if, in fact, one were to answer that going from a term to a preterm population is never indicated, and so that, in fact, that's no. That's probably one of two instances where a simple no should suffice, because I think that should be clear to everybody what "no" means.

On the other hand, if it is "depends" or "maybe," then it would be very helpful if one provided some criteria and rationale for, and if possible even examples. If it is "maybe," when would it be no and when would it be yes? What are the criteria for a yes or a no and what would be the rationale for those criteria? If possible, can you provide an example of a yes or a no.

The reason for wanting to cover all three

questions at one time by each individual is to help each of us be as consistent in our responses as possible, both as a group and individually. I think it would not be as efficient if we were to go around the table three times.

So if I don't hear any objections to that procedure, then we'll start.

[No response.]

DR. GARZA: Okay. Then let me see if I can get the list. The three invited liaisons, non-voting consultants, that I have are Dr. Clemens, Garlick, and Giacoia, and then Dickinson and Scholz. I will be going to all non-voting members first, so we will begin with Dr. Clemens, then Dr. Dickinson, Dr. Garlick, Dr. Giacoia, and then Mr. Scholz. Mr. Scholz is not here. Should he come in before, we will surprise him.

[Laughter.]

DR. GARZA: Dr. Clemens?

DR. CLEMENS: Do you want to start with question three?

DR. GARZA: Question one, and then

question two and then question three.

DR. CLEMENS: We have taken the time last evening to prepare a written response to get the discussion going. Thank you very much, Bert, for the opportunity. There is a handout--

DR. GARZA: When you say "we," can you--

DR. CLEMENS: The infant formula manufacturers represented at this meeting. I am the representative for those manufacturers.

DR. GARZA: So this is not your personal response but a group response?

DR. CLEMENS: It's a group response, yes.

DR. GARZA: Is that appropriate? I don't know. Can we have group responses?

DR. CLEMENS: I'm a representative for that group and my name is on here, so I'm accountable for everything that's said, so--

MS. HAYDEN: We know that.

[Laughter.]

DR. CLEMENS: Thank you, Linda.

DR. GARZA: I just want to make sure. Thank you.

DR. CLEMENS: There should be three packets going around the room. Thank you, Bert. We want to be succinct and direct, perhaps a launching pad for the discussion.

Dr. Anderson made a presentation yesterday. She mentioned a decision tree process. Dr. Dwyer had indicated what are the components of that decision tree process, and I believe Dr. Stallings indicated the same thing. So we elected to assemble some brief concept thought or thought process which are involved in that decision tree process. We've entitled this as a draft, a generalization decision analysis, and in this decision analysis we've outlined five basic questions in response to your question.

The answer I indicated there at the top in the five bullets. First of all, be sure that every ingredient is GRAS or an improved food additive for intended use. In this case, the intended use is infant formula. Fundamentally, we look at a go/no go operation, as you can see here.

Fundamentally, we ask ourselves, what do

we know about the digestion, absorption, metabolism, and excretion of the ingredients in preterm versus term infants and the decision tree is quite clear. Are they meaningful or not meaningful, and this is based on our experience and in the literature and clinical evidence.

Then looking at the protocol, what is the protocol for a preterm study? Again, what do we know? Is the study to be initiated in late, preterm, or extended into term? Often, this is the case of preterm infants are studied. They'll be looking at kids which are physiologically mature. These are healthy, preterm infants, if preterm infants are to be used.

Often, the case may be that--or frequently, the case may be that preterm infants are started and are at 32 or 34 weeks of age, gestational age, and they will continue on into, if you will, 52 weeks, and so clearly, they will follow that course. Dr. Lien indicated that yesterday.

What is the quality of the study, of the

data? We emphasize that we follow good clinical practice and that includes clinical practice, the statistical design, such as those components involving power calculations. Relative to statistical analysis, we have to say are those data, those practices, and those respective studies which are public domain, are they relevant or not relevant? Are they meaningful or not meaningful? It's part of the decision tree process.

Is a preterm infant consuming more nutrients per kilogram of body weight, and again, are the data meaningful or not meaningful relative to term? And if so, we ask ourselves, what additional supporting data are available, both in-house and outside? Is there a great deal of data? Are there international data from which we can glean information?

Are there studies and other matrices, whether it be liquid matrix or powdered matrix? And certainly, are there clinical studies available in the public domain that other manufacturers have provided which could be leveraged to use as the

total totality of data as indicated in the discussion.

I trust that this fundamental review process, at least thought process, is of value as we go through the question.

Number two--

DR. HEUBI: Roger?

DR. CLEMENS: Yes, Jim?

DR. HEUBI: This addresses preterm to term, but there's nothing in here about term to preterm. Are you basically saying that those shouldn't be applied in any way to preterm infants?

DR. CLEMENS: Thank you, Jim. This is the most common event here. We typically don't go backwards because of the unique nutrient requirements for those kids. I think Dr. Hierd had indicated yesterday that, clearly, the preterm are the most vulnerable. You look at both velocities and other issues, and clearly, that makes sense to look at it this way as opposed to the other way around.

DR. GARZA: Yes, Dr. Russell?

DR. RUSSELL: Yes, thank you. The other clinical studies and other matrices, wouldn't it also depend on the similarity of those matrices?

DR. CLEMENS: Or even the dissimilarities of those matrices.

DR. RUSSELL: Or the dissimilarity.

DR. CLEMENS: That's right.

DR. RUSSELL: So it's not just that other studies exist and other matrices.

DR. CLEMENS: That's correct. We look at the totality of data available.

DR. GARZA: Dr. Dwyer?

DR. DWYER: Would the healthy/ill-healthy comparison fit in a similar matrix?

DR. CLEMENS: They would fit into this matrix. Typically, we look at healthy preterm babies. That's the focus of these kind of generalized studies. These kids are not compromised other than gestational age. That's why we emphasize in this case late preterm infants.

DR. GARZA: In clarification on that point, is the mean then of the population the 50th

percentile when they enter the study, or are they significantly below that? Your definition of healthy then is?

DR. CLEMENS: Their Apgar scores are appropriate. I can't tell you exactly where their percentiles lie here, but--

DR. GARZA: By healthy, you mean they have no clinical condition--

DR. CLEMENS: No clinical condition that would predispose them to be excluded. Certainly, they're typically above the tenth percentile.

MS. GRANT: This is Sigmar Grant. Can I ask a question? Are these hospitalized infants or are they infants sent home?

DR. CLEMENS: At 1500 grams, they usually go home. Many of these kids are 1500 grams plus. They are ready to go.

DR. GARZA: That's all right. That's the response. You all may respond when you wish.

DR. STALLINGS: I think one of the things, I think one of the hard parts that we are grappling with that's sort of central to this is is there

any--are we really only designing formulas for healthy preterm babies, for just sort of the last few weeks of a hospitalization, and, in fact, those formulas are necessary to get babies to that point, and, in fact, we heard yesterday, maybe given to babies as small as--

DR. CLEMENS: Four hundred grams.

DR. STALLINGS: --as 400 grams, which is pushing it, that they even have a little intestine to absorb anything--

DR. CLEMENS: Sure.

DR. STALLINGS: --but that whole concept really is central to what we're doing, so I think we have to keep that in mind. I don't have a lot of answers to that, but talking about--I mean, it's been very good for us to realize that these studies are being done on the healthiest, most mature preterm babies.

DR. CLEMENS: That's correct.

DR. STALLINGS: And I think one of the things that might come out of this whole process is, in fact, we are feeding--these formulas are

very important to the survival and the growth of those babies at a much younger age and under clinical conditions where we would all agree that they are not healthy. Consequently, we have no data on these products in a place where they're also intended and as clinicians we desperately need them.

So it's an interesting piece that I think has come out of this, and except that that's where the studies are being done and the inclusion and exclusion criteria that we use drive us to enroll those babies in these trials. But they're not the only intended use.

DR. CLEMENS: You're right. Clearly, if you look at the data, very young preterm, if you will, the kids less than, say, 32 weeks, even much younger than that, 24 weeks, clearly, that's a separate set of population which may not be applicable, and I think Dr. Lien made that presentation yesterday. Clearly, if you look at the healthy term baby, it may well be applicable in some cases.

DR. GARZA: Before we move to question two, I want to make sure that each of us understands that, in fact, questions regarding clarity so that, in fact, you better understand the recommendation or response, are fine. But going beyond that, I'd ask each of you to limit whatever comments or answers you would like to provide to the questions to when your turn comes. Otherwise, it's going to be very difficult. It's not the time to try to change somebody's mind or change the nature of their response, but, in fact, to be informed by it and then you are certainly free to formulate your own response as the time comes.

DR. TAYLOR: Taylor, FDA. Is it okay if I ask a question just for clarity?

DR. GARZA: Just for clarity, yes.

DR. TAYLOR: And it is just for clarity. As written, it's not clear to me how this would be used in a review setting. Should the agency be using only the most meaningful? Is the agencies supposed to use sometimes most meaningful and sometimes least meaningful? What if they're mixed?

In other words, as a practical tool, I would ask for some clarification as to what this means for informing our review process and decision making.

DR. CLEMENS: Let me respond to that. I would offer that after this meeting, we would do a follow-up and provide documentation to Dr. Garza to provide additional detail to this response.

DR. GARZA: Okay. Dr. Dickinson?

DR. DICKINSON: For clarification on the point of what the Infant Formula Act and the infant formula regulations cover, I did read the regulations before coming to this meeting, and I apologize for not being fully familiar with infant formula regulation, but I see that there is such a thing as an exempt formula and I'm wondering whether some of the questions about the very sick infants and the very seriously premature infants, whether, in fact, they're not intended to be covered by these regulations and whether those are exempt conditions under which a special formula would be prescribed. It may be the same formula, but the formula would be selected and prescribed by

the physician.

DR. GARZA: Or modified at the hospital.

DR. DICKINSON: Yes. In other words, does the regulation and the Act cover primarily products marketed for healthy infants?

DR. TAYLOR: My understanding of the regulations is they cover those that are not exempt, and exempt formulas are listed. So to the extent that these would be formulas intended for non-exempt situations, the answer is it still applies, but there are exemptions for PKUs.

DR. GARZA: Any other questions regarding the response to the first question?

[No response.]

DR. GARZA: Okay. Number two?

DR. CLEMENS: Again in your handout that just went around the table, at the top of the handout it says, question two. The question is restated.

In response to the question, yes, it is appropriate to use those data to support growth. If one is doing an appropriate power analysis for

growth, the studies are not powered to detect relatively low differences in adverse events. However, this does not negate the power of the study with respect to supporting growth. If it differs between study groups and a number of adverse events is observed, whether or not the study has power to detect that rate, the clinical significance of the difference must be evaluated through good clinical practice.

DR. GARZA: Any questions regarding this response?

[No response.]

DR. GARZA: Dr. Clemens, am I correct then in saying when it reads, if a difference between study groups, that you're not limiting that difference to one that is statistically significant, whether it's the power is there or not? If there is a difference, then one ought to look at it and determine its clinical significance?

DR. CLEMENS: That's correct.

DR. GARZA: Any questions, other questions?

[No response.]

DR. GARZA: Okay. Number three?

DR. CLEMENS: Again in your handout, the top is indicated by question three. The question is stated. I have a rather simple response.

Our typical clinical experience suggests that the normal attrition rate in a growth study approximates 25 percent. The assessment of physical growth is relatively insensitive to attrition rate. For example, study groups with ten versus 20 percent attrition rates do not have the potential to sufficiently bias the assessment of physical growth rates to change the outcome of the study. This is a matter of statistics, and if you'd like, and perhaps in a subsequent documentation, we can go through the mathematics of what it takes to shift the apparent growth rate. The bottom line with this is that all data are relevant.

DR. GARZA: Any questions? Dr. Heubi?

DR. HEUBI: I guess I have to ask you this question, Roger. If, and since you're the industry

liaison, if a study were powered based upon a 20 percent attrition rate, and because of your attrition rate you lost more than your 20 percent, what would be the stance of the sponsor in terms of would they abandon the study or would they recruit additional subjects or what exactly would happen in that context?

DR. CLEMENS: Good point. Good question, Jim. Every manufacturer manages that differently and that situation is anticipated at the front end of the study, so it's not a reactionary approach. Many times, you can't recruit sufficient subjects or they drop out. Additional subjects may be recruited, or, in fact, it may be discontinued and then you account for the attrition rate.

The panel on the statistician and the advisory group with which they're working, they may take either one of those approaches. Typically, they account for the attrition rate and they go with it. If more than that drops out, still, they look at statistical analysis. Is it appropriate? Typically, your dropout receives a normal

distribution. Clearly, you're not going to skew the data because the typical dropouts are not at one end or the other end.

So, again, if you look at the mean, the mean is not affected unless you skew it by dropping out of the top or dropping out of the bottom. So, again, all the data are relevant.

DR. GARZA: Are there any other questions by other members of the group?

Dr. Clemens, in reading the question, the question speaks to differences in rates between the two groups, not the overall attrition rate as the response seems to address. Can you clarify that for me?

DR. CLEMENS: You might say that the ten and 20 percent might be perceived as differences in rates, and, in fact, if you look at the result of that, of the attrition rate, they do not impact on physical growth in this case.

DR. GARZA: So the response is intended to deal both with equivalent attrition rates among both groups, where you may then encounter the power

problem that Dr. Heubi alluded to, as well as to issues of randomization when, in fact, you have significantly different--of the magnitude that was discussed yesterday--between differences, or between groups in terms of attrition rates--

DR. CLEMENS: That's correct.

DR. GARZA: --where you have a four- or five-fold. Okay. Any other--

DR. DWYER: Maybe this is the wrong time, but couldn't that also be handled by just doing intent to treat analysis?

DR. GARZA: Well, we went through that. As long as you could follow up the reasons why.

DR. CLEMENS: Agreed.

DR. GARZA: But the reason I asked is because, in fact, this doesn't speak to those issues, at least in my reading of the response, and I wanted to make sure that that was clear.

Any other questions?

[No response.]

DR. GARZA: Thank you very much, Dr. Clemens.

All right. Then we'll move on to Dr. Garlick.

DR. GARLICK: I'm also speaking for a small group of us who had been together yesterday and I think we were all in total agreement on these points.

The first one was a general statement, which is that infant formulas seem to us to be a special class, more like a drug than a food. That's just a general statement.

In terms of the individual questions, the answer to the first question is presumptively no. We felt that term studies must be done in term infants unless there's a very strong justification that this is not necessary. In these cases, the requirement to do studies in term infants could be appealed to the FDA, so we'd recommend that the appeal be reviewed by a panel of experts.

And secondly, ideally, studies that could potentially need to be done in both term and preterm infants could be reviewed by the FDA prior to initiating any studies, so at least the plan

could be designed so that they wouldn't initially start off in preterms if, in fact, they were going to have to be done in terms anyway because that would just duplicate the effort.

So that's our conclusion on the first point, if there's any questions.

DR. GARZA: So to the first point, does that mean from one population to another or the response to the first question?

DR. GARLICK: That was the response to the first question.

DR. GARZA: Okay. Are there any questions regarding that response? Can you elaborate a bit on the rationale for the response, or would you prefer that somebody else do that?

DR. GARLICK: The feeling was that term and preterm are metabolically different. They handle nutrients differently and, therefore, there was no reason--there was no good reason not to do the studies in the group of infants for which the formula was designed.

DR. GARZA: Any questions? Dr. Hotchkiss?

DR. HOTCHKISS: Just a point of clarification. Who is the small group?

DR. STALLINGS: It was our dinner group.

[Laughter.]

DR. GARZA: So it was an ad hoc group.

DR. STALLINGS: It was an ad hoc, not bound by anything else other than the search for a dinner table.

DR. DWYER: What was that liquid that was on the table?

[Laughter.]

DR. GARLICK: Only water.

DR. STALLINGS: It wasn't infant formula, though we did use it as an opportunity to continue the discussion. So you'll probably hear modifications, but that was the report.

DR. GARZA: All right. Response to question number two?

DR. GARLICK: We were not able to answer this question definitively. We felt that there should be an independent board to monitor and assess adverse effects because, potentially,

adverse effects do have the capacity to influence the outcome if those infant--in terms of growth, because if those infants that were not growing were the ones that were showing the adverse effects, then they influence the statistics.

We also felt that such guidelines for infant formula studies should be created for reference regarding sample size, handling of adverse events, et cetera. This is to enable reporting adverse events to be much more rigorous and, therefore, the data much more useful. At present--well, if there are no regulations on the--very strict regulations on this, it depends on the individual running the study as to just how adverse an adverse effect is and it needs to be more--a more rigorous approach to that.

Also, there needs to be a better established mechanism for reporting a post-marketing adverse event because that's the time when adverse events actually turn up, for the most part. They don't usually turn up in great numbers at an earlier stage.

We're suggesting these measures to protect the industry, basically, from any subsequent claims that they might not be reporting adverse events appropriately. So that's the second question.

DR. GARZA: Okay. Any questions of clarification? Dr. Clemens?

DR. CLEMENS: Jim is smiling, so, yes, I'll respond. Rog Clemens. You should know that while it's not mandated on the AE reporting structure what the agency--that each of the manufacturers in compliance with international standards and SOPs has a rigorous reporting structure to accommodate adverse events in any clinical trial which they conduct.

Secondly, we may not have a post-marketing surveillance program in the United States, but we do have a mandated complaint program in the United States. It's the only one in the world in which customers or consumers as well as the medical community can contact the manufacturer directly and file either a physical complaint about the issue or may file a medical complaint about it, and those

medical complaints are, in fact, mandated to be reported to the agency. So in that regard, there is a sense of post-marketing evaluation involving the formulas.

DR. GARZA: So your question of clarification is?

DR. CLEMENS: Dr. Garlick had indicated the required post-market evaluation and I wanted to reassure him that, in fact, there is a system in place at this point. He suggested that there should be an AE reporting system and I wanted to assure him that, in fact, there are guidelines set up by the industry that has an AE reporting system in place.

DR. GARZA: So you want him to clarify the need for one given what you've said?

DR. CLEMENS: I think it's assumed--maybe that's not the proper word, but that we, in fact, have something in place, even though it's not mandated by the FDA.

DR. GARZA: Dr. Garlick, do you want to respond?

DR. GARLICK: No.

DR. STALLINGS: Roger--

DR. GARZA: Dr. Clemens has already spoken, so--

DR. STALLINGS: Well--

DR. GARZA: Again, I don't want to reopen the issues. That's why we went through a period saying, now, do you have any other questions or comments about these three, because we're going to start getting people's responses. Unless--that's why I asked him specifically. I really would like to ask each of us to refrain from commenting--

DR. STALLINGS: Okay.

DR. GARZA: --trying to change people's minds. There was an opportunity to provide as much information given to us in the earlier part of the meeting so that, in fact, we can--I think it would be totally appropriate to say, given the structure, why, in fact, have you recommended something to replace it? In this case, I might have expected Dr. Garlick might have said, well, it's not mandatory and we think that a mandatory is needed.

That would be the difference.

But try to focus on issues of clarification so that you can better understand the response, and the only reason for starting with non-voting members is that we feel they have a special expertise that, in fact, will inform each of us as we formulate our own responses.

DR. GARLICK: As a matter of clarification on my own behalf, I didn't respond to that question because I thought that my committee, my co-members from last night would be in a better position to comment on that when they made their own statements.

DR. GARZA: In terms of that, it's my understanding that whatever happened last night has no bearing in terms of this committee's decision. You can certainly use it to get new information, to inform yourselves, but, in fact, obviously it wasn't an ad hoc group getting together under the auspices of anything other than having a dinner discussion and using that as an opportunity to get better informed.

DR. STALLINGS: Which is all that it was.

DR. GARZA: Thank you.

DR. HEUBI: That's absolutely correct. To speak for Peter, because he was going to defer to us, I think really what we thought was that it would be appropriate to have some mandatory reporting program for infant formula like MedWatch that was publicly accessible so that under the sunshine laws or whatever they call those things, because I'm not a bureaucrat, that information is available to the public.

DR. GARZA: What I'm trying to clarify is that what we heard was Peter's response. This group will expect responses from each of you as individuals.

Any other points of clarification for question number two?

DR. STALLINGS: Maybe I can direct this to the FDA, but my question is do you see the adverse event reporting in a direct way when you do your 90-day review of a study that's already been conducted and closed?

DR. GARLICK: I'm sorry, could you clarify that?

DR. STALLINGS: Because I think part of the confusion on my part is whether you have access to all of that information to make your own decisions as part of your 90-day review or if the decisions are made prior to that and it's not brought to you in full disclosure.

DR. TAYLOR: Just to clarify, you mean as part of the 90-day package, are the adverse event reports made available to the agency?

DR. STALLINGS: I think, if I understand it correctly, all that the FDA gets is the information provided by industry for your review as a pre-marketing review. I didn't know if you-- because I know they're collected--

DR. GARZA: It's my understanding that, in fact, at least as I heard an answer to a previous question, that information is part of the packet, but it is there at the discretion of the individual that's putting the packet together.

DR. STALLINGS: Which would be--

DR. GARZA: There's no check box that says, all adverse events, how are they done. There are common practices, good clinical practices that govern that, but it is not a mandated statutory, regulatory requirement that meets a priori guidelines.

DR. TAYLOR: And after checking with our brain trust to be sure we were right, it varies. Some manufacturers provide it. Others do not.

DR. GARZA: The response to question number three?

DR. GARLICK: The presumptive answer is no. As was discussed yesterday, high attrition rates maybe should be regarded as an outcome. It's perfectly possible that a higher attrition rate could result from some reaction to an adverse--a minor adverse reaction to the formula itself or some rejection by the infant of the formula. Therefore, taking them out of the total group will affect the outcome and the remaining infants may well be the same, whereas if they take as a total group, it could be possible they could have been

different. So I think it's important that the answer is no.

In addition to this, when possible, the reasons for the dropout should be ascertained, because obviously the previous conclusion, which was that it could affect the result, is entirely dependent on the reasons for dropout. If it's to do with acceptability, then, yes, it might affect the outcome. But if it's because, by sheer chance, parents are moving out of the area in different numbers for the different groups, then obviously it won't. So reasons are an important issue if it's possible to get them.

It's also, of course, presumed that all studies will be powered to indicate a typical attrition rate so you know it's becoming much higher than you expected.

These recommendations are specifically referring to studies with large differences in attrition rates, so that it should be possible to detect those, to show that those are different.

DR. GARZA: Okay. Any questions?

[No response.]

DR. GARZA: Okay. Thank you very much.

We went out of order. I should have asked Dr. Dickinson, perhaps, to speak before Dr. Garlick, but I didn't have my notes with me. Someone whispered Garlick in my ear and I didn't look at them.

DR. DICKINSON: If someone had whispered Echinacea, what would you have done?

[Laughter.]

DR. GARZA: Probably run for the closest herbal food store or something, I guess.

DR. DICKINSON: I'm responding as an industry representative. I have 30 years of experience in food and drug regulation issues, but not in infant formula in particular, so forgive me if I'm not up to speed entirely on infant formula issues, but I have made an effort.

I'd like to distinguish on the first question between relevance and generalization because I found it troubling some of the discussion yesterday seemed to imply that a study done on one

population group might under some circumstances just be transferred wholesale to a different population group. I'd like to refocus my answer, at least, in terms of relevance.

I would say that in response to the first question, study on any infant population has very likely relevance to findings that might be found in a different population and the degree to which it is relevant will depend on some of the things that were outlined in Dr. Clemens' response and also that we heard from several of the spokespeople who presented to us yesterday.

It seemed to me in listening to that discussion that there is, at least in the case of many nutrients, a good understanding about whether there are differences both in requirements and in utilization in preterms versus terms or in healthy infants versus non-healthy infants and that whole body of evidence will, of course, need to inform the decision about whether a study is relevant to the other population.

I guess my inclination would be not to

focus on the term "generalizing" but to focus on the relevance of the study, and I think that in each of these cases, the responsibility to make the argument that it is relevant rests with the manufacturer making the submission and that while we--while you, at least, may wish to give the FDA some guidance in terms of what things they would look at in making that determination and in agreeing or not agreeing with the manufacturer, I would think that in the end, it comes down to a requirement that the manufacturer has to make the case in submitting this evidence as to whether it does or doesn't apply to a different population and if it does, why it does.

I would think that between the experts available to the industry and the experts available to FDA, that they're just going to have to work that out. I do not believe there's a simple yes or no response to this.

DR. GARZA: Any questions?

[No response.]

DR. GARZA: If not, let's move on to

question two.

DR. DICKINSON: I would take question two and question three together, and my response to them is similar. I think that, depending on the circumstances, there may be conditions under which changes--differences in adverse event rates in the two groups may be highly significant, depending on how serious the events are and how big the differences are.

And again, my basic take on this as a regulatory issue is that this is a matter where the industry will bear the responsibility for making the argument to the agency about whether the adverse events are or are not relevant in determining whether the findings are meaningful, and likewise, whether the attrition rates, if there are differences in attrition rates, whether those are relevant or whether they cripple the study or do not cripple the study in terms of its relevance for the purpose for which it was done.

DR. GARZA: I'm sorry, I was speaking with Linda and I lost track. Were you doing question

three or two?

DR. DICKINSON: I was doing two and three together.

DR. GARZA: Two and three together, okay. I understand the response, then. That's the part I missed.

Are there any questions?

[No response.]

DR. GARZA: Okay. Then we'll move to Dr. Giacoia.

DR. GIACOIA: I'm going to be succinct. First of all, it's usually--say that the children are not miniature adults. I will add that very low birthweight babies are not miniature full term babies. In general, I think that clinical trials have to be based on the population that it's intended to and also that the sample from that population must be representative--it be a representative sample of the population.

So if the answer is extrapolated from preemies to full terms, my sense is that should not be unless there are very specific circumstances,

and it would have to be very stiff guidelines, the degree of prematurity that will be allowed to represent term babies.

On the issue--and the same line here, I was somewhat bothered by the stratification of low birthweight babies based solely on birthweights rather than gestational age. I think here one introduces biases that is not done in other studies in this population.

Also, into defining population, if you only define by pure birthweight and not other factors, such as socioeconomic factors, that can influence outcome, and I think I'm bothered particularly with the idea of study populations which are not representative from the population it is intended to. So to just select a group of preemies which are very healthy, it would not serve a good purpose.

On the question of the products, I think that I'm bothered to try to think into the future whether changes in formulations will, as science advances, will be at this time unpredictable and,

therefore, I'm bothered to try to do this type of thing unless we simulate those drugs when we have some of the so-called "me too" drugs, which are not really very much difference between them, in which case an exception can be made.

The other issue that bothers me is definitions of healthy and diseased, things that are very difficult in the sense that, number one, it needs to be recognized where the patient got over the disease at the time of the study versus those which continue to be having difficulties, such as it be the children that will have significant problems. So you take a group of the very--

DR. GARZA: You mean bronchopulmonary dysplasia?

DR. GIACOIA: Yes, right. So--

DR. GARZA: I'll ask everybody to try not to use acronyms because other non-experts may not be--

DR. GIACOIA: Yes. By the same token, there is a subset of term babies who are sick and

they're not with a metabolic disorder, but they have a number of other conditions that might be present.

Now, as far as the question on adverse events, I think the issue here is, first of all, the--

DR. GARZA: Before we move on to question two--

DR. GIACOIA: Oh, I'm sorry.

DR. GARZA: --let's see if there's any points of clarification that people would like to raise to your response to question one.

[No response.]

DR. GARZA: Okay.

DR. GIACOIA: As far as adverse events, first of all, we all recognize that many of these events are totally unrelated to either a drug or a formula and, therefore, it will be important to understand the nature of those events. I think that it is important to characterize the most degree of severity and I'd like to see whether the FDA will have some criteria that will apply to this

particular situation.

I totally disagree with the idea that this is, quote, "a system is in place." This has proven to be a disaster as far as drugs are concerned, and there, we have high mortality related to that particular issue. Voluntary systems have been a dismal failure. Some individuals--for example, in the case of drugs, it has been estimated that one physician every 600 years reports an adverse drug event. That means that the whole thing is not present.

So the other thing, there's a lot of issues related to post-marketing unless it's starting out and it's really looking into detail, because I think that, as I said, I doubt very much the situation in nutritionals is any better than the situation in drugs. I do support the idea of having a DSMB for measure life threatening situations, or serious events. I don't think they should be across the board for anything. That's question two.

DR. GARZA: And for clarity, you meant

that they were physicians reporting, physician years, not individual physicians do this every 600 years?

DR. GIACOIA: Yes. I don't think they are--

DR. GARZA: But in terms of a physical definition of physician years, yes. All right. Any other points, questions of clarification?

[No response.]

DR. GARZA: Okay. We'll go to number three. Thank you.

DR. GIACOIA: Number three, again, I agree it's a statistical situation and I think the rules of the game cannot be changed and review statistically and calculate what the attrition rate should be, you really do justify why this is beyond that particular rate. And also, I'm very bothered to the idea to have a systematic bias in which a bioequivalence that is not present may be demonstrated by the difference in attrition rates or whatever situation. So, therefore, the composition of those individuals are excluded must

be known, and I think that will be a situation DSMB would be present to pass judgment as to whether it's adequate to accept the study.

DR. GARZA: Any questions?

[No response.]

DR. GARZA: All right. Then I'd like to get sort of an informal poll from the committee. It's ten o'clock. We can either take a very short ten-minute break, because I don't want to interrupt the voting session. We've heard from FDA, from the non-voting members of the committee, and so the information session to guide each of you in your responses is now over and so it's a nice break point. We can either do it now or--go now? I don't see an overwhelming. Do you want to break? All right. We will be back at 10:05.

[Recess.]

DR. GARZA: It's 10:05. If I could ask the committee members to take their seats, we will start. I will begin--

[Pause.]

DR. GARZA: We will start with Dr.

Anderson, and again, I would ask that he take them in order and we'll allow some time for clarification after each question. Dr. Anderson?

DR. ANDERSON: Generalizations of results from clinical trials of one infant formula in a specific population to the same or different formula in another population will have to be judged on a case-by-case basis. In most cases, results obtained from studies performed in healthy term infants will not be adequate to inform what would be expected to be observed in preterm infants. Likewise, studies performed exclusively in healthy infants or exclusively in those with metabolic or disease conditions are unlikely to provide adequate information regarding the formula's use in another population.

Nevertheless, there are likely to be circumstances where the state of knowledge is such that the findings of a study in one group of infants would generally be agreed to be directly applicable in another setting, although I don't feel competent to judge when such circumstances may

exist.

The FDA may wish to consider the establishment of an advisory panel of experts which could advise the FDA during or perhaps before the 90-day pre-market notification process period. The panel could be expected to assist the FDA to determine in cases where an infant formula submission depends in large part on the generalization of data from clinical studies in other populations and/or with other formulas whether the state of knowledge is such that the formula submission should be considered adequate or whether additional information is thought to be required.

DR. GARZA: Any questions?

[No response.]

DR. ANDERSON: The agency understands the response?

[No response.]

DR. ANDERSON: Okay. Comprehensive reports of clinical trial adverse events should be part of every 90-day pre-market pre-notification

packet. There may be cases when clinical studies demonstrate that a new infant formula supports normal physical growth under its intended conditions of use, but the available data raise clinical concerns about the rate of adverse events in those receiving the new formula.

The FDA may again wish to consider the use of an advisory panel of experts to make recommendations regarding the clinical significance of the observed rates of adverse events. After this review, the FDA may choose to consider the formula submission adequate or may request that additional information regarding the rate of adverse events associated with the new formula be provided.

DR. GARZA: Okay. Any questions?

[No response.]

DR. GARZA: All right. Number three?

DR. ANDERSON: When large differences in attrition rates between study groups are observed in a clinical trial, one of two situations exists: The difference observed is due by chance alone, or

the differential attrition rates are a direct effect of the interventions. Because complete data from those who fail to complete the study are often lacking, the benefits derived from randomization and blinding in the unbiased assessment of treatment effects will likely be lost in the setting of large differences in attrition rates.

Therefore, unless there is compelling evidence that the differential attrition can be attributed to factors independent of treatment, such studies should not be considered adequate to conclude that a new formula supports normal physical growth under its intended conditions of use. An advisory panel of experts may be of assistance to FDA in its assessment of when differences in attrition rates are, quote, "large," and whether the differences can be reasonably be considered to be independent of treatment.

DR. GARZA: Okay. Any questions?

[No response.]

DR. ANDERSON: Dr. Garza, I have one more thing I'd like to say, if I may.

DR. GARZA: Surely.

DR. ANDERSON: Experience with the use of a panel of experts in the review of new infant formula submissions would be expected to develop a body of case reviews which should clarify the appropriate circumstances where generalization of study results is appropriate, clinical concerns regarding adverse events are unfounded, and when large differences in attrition rates can be ignored.

In addition, if a panel of experts is to be considered, the 90-day pre-market notification process period may be too short to provide adequate input from and advice to the FDA. The FDA may wish to consider the establishment of a, quote, "intent to market" process that begins prior to the 90-day pre-market notification process period which informs the FDA of the types of data which will be used to provide assurances, including whether generalizations of results from clinical trials could be a major component of the submission and whether any clinical concerns regarding adverse

events or major differences in attrition rates exist in the clinical trials to be submitted in support of the assurance.

DR. GARZA: Any points of clarification regarding that last statement?

[No response.]

DR. GARZA: All right. If not, we'll go on to Dr. Baker.

DR. BAKER: On the first question, I believe that the answer to the first question is that it depends, but I would like to qualify this by saying that the modus operandi should be that generalization is not allowed and the exception should be that it is allowed. I base this on the fact that it's wrong not to do a study that's indicated, but it's also wrong to do a study that's not indicated. I think that the onus on proving the studies are not indicated should fall on the industry and that they should provide evidence for that.

In support of not doing a study, I think that all relevant data should be submitted and

brought into play, and I'd like to emphasize all and relevant, "all" meaning data that even though it's not generated in the general way, in the usual way, it should be admissible, and "relevant," there should be some ascertainment of whether a study or data is really relevant or not before it's taken into consideration.

I'd also like to emphasize the word "data" in that I would say that it's not necessarily--this information does not necessarily have to be a study but could be experience, for instance. That's question one.

DR. GARZA: Any points of clarification?

[No response.]

DR. GARZA: Dr. Baker--I'm sorry, go ahead.

DR. STALLINGS: Dr. Baker, tell me more about the use of the experience. How might you envision that, rather than data collected in a protocol setting?

DR. BAKER: Just as an example, for instance, the DHA and AA question, there is a large

body of experience that's already available in the world that's out there. That should be--

DR. STALLINGS: Not in literature.

DR. BAKER: Yes. The experience in Europe, for instance, it's not in the literature but it's long and fairly extensive.

DR. GARZA: Can you elaborate a bit, Dr. Baker, on the rationale for the default being no?

DR. BAKER: The reason for the default being no is that I think, as other people have stated, that populations are really not the same, that a 24-week gestation preterm is not the same as a 32-week gestation preterm and that preterm is not the same as term, and even that term is not the same as at six months. So definition of population is difficult and needs to be looked at, but certainly generalization--these are different populations and generalization should not be assumed.

DR. GARZA: And the difference, I'm assuming, physiologically or metabolically?

DR. BAKER: Right.

DR. GARZA: Are there any other questions?

[No response.]

DR. GARZA: If not, let's go to number two.

DR. BAKER: Number two, it's my opinion that adverse events should be taken into account when judging an infant formula. I believe that my answer is a part of the clinical study process. If you're not going to take adverse events into account, why are you tracking them? So I think that they definitely need to be taken into account, and as a part of this, I think that what other people have suggested, an advisory board may be useful to decide whether an adverse event is happenstance versus a real event.

DR. GARZA: Any questions?

[No response.]

DR. GARZA: Number three?

DR. BAKER: Number three, attrition rates. I view this as largely a statistical problem. I believe that attrition rates are important, that they are an outcome measure of the study and,

therefore, ought to be taken into account in assessing the validity of the study. I also believe that most of these problems with attrition rates could be dealt with a priori via your statistical support.

DR. GARZA: Any questions?

[No response.]

DR. GARZA: Thank you very much.

Dr. Denne?

DR. DENNE: In answer to the first question, sort of a strong presumptively no. Again, the general principle is that studies ought to be done in the population for which the product is designed. There are major differences in physiology, metabolism, nutritional requirements, and growth, including body composition, between preterm and terms, and so they really are not interchangeable and, therefore, preterm infants cannot be used, or data in preterm infants cannot be used to actually model term infants without some term data.

In addition, this is really not a healthy

population. We have talked a lot about healthy preterms, which is, frankly, kind of an oxymoron. They're healthy relative to the ventilated very immature individuals, but they're certainly not healthy relative to normal term infants.

In addition, nutritional studies in preterm infants really differ in design. In particular, there are at least some time periods of controlled nutritional intake in preterm studies which really doesn't mirror the term population.

So under almost all circumstances, I would answer that question as no. In the event that preterm data, the industry wanted to substitute preterm data for term data, I believe a strong scientific justification would need to be made prior to beginning a study in preterm infants.

DR. GARZA: Any questions?

DR. BAKER: I have one question. You said that the study, if you wanted to generalize to term infants, you needed to say you were going to do that at the time you were studying your preterms?

DR. DENNE: Right. I mean that if there

was a justification to substitute preterm for term, then that ought to be scientifically justified before beginning your study in preterm. In other words, just having data on preterms isn't justification enough. It should be done prior to initiating a study.

DR. GARZA: All right. Number two?

DR. DENNE: In response to this question, I'll echo most of the previous comments, and that is that I think that, in general, this needs to be assessed by an independent board and assessed in relationship to the severity and frequency of adverse events. The board should advise the agency about whether there is concern enough to continue or provide additional study or whether some of these adverse events could be explained and the product approved. But again, I think an independent board, advisory board, may be the mechanism by which this could be handled.

DR. GARZA: Any questions?

[No response.]

DR. GARZA: Number three?

DR. DENNE: For number three, I think I would like to sign on to Dr. Anderson's comments. I don't think I could say it any more succinctly or clearly than he did. The differences in attrition rates between groups should be considered as outcomes. They need to be evaluated by an outside independent board, and again, presumptively, if there are major differences, that should be viewed as an inadequate study.

DR. GARZA: Questions?

[No response.]

DR. GARZA: Okay. Dr. Heubi?

DR. HEUBI: You don't get to go first?

DR. GARZA: I don't get to go at all.

DR. HEUBI: The answer to question number one, the answer basically categorically from my perspective is no. Under selected circumstances, the FDA can convene an expert panel to review requests for formal changes based upon studies in one group of infants for comparison to another, that is, for preterm to term.

The question of waiving a requirement for

study in target populations must be based upon strong scientific grounds. This is not different from what's been said before.

DR. GARZA: Any points of clarification?

[No response.]

DR. GARZA: Hearing none, let's go on to number two.

DR. HEUBI: Number two, formula studies should not be powered to detect differences in adverse event profiles. To ensure adequate protection of subjects in trials, independent DSMBs, Data Safety Monitoring Boards, should be empaneled to review all adverse events with focus on frequent and serious unanticipated events. Post-market surveillance should be enhanced to ensure safety, since only with wider use of formula after marketing can significant adverse events be identified.

DR. GARZA: Okay. Any questions?

[No response.]

DR. GARZA: All right. Third?

DR. HEUBI: Large differences in attrition

between study and control groups may suggest problems with the study formula and, therefore, should be carefully investigated. Studies should be powered for an anticipated dropout rate. If rates of attrition in the study group exceed anticipated losses for which sample size capture were made, the results from the study should be considered suspect.

DR. GARZA: Any questions? Dr. Clemens?

DR. CLEMENS: Rog Clemens. Jim, what would you consider strong scientific evidence?

DR. HEUBI: I think strong scientific-- you're referring to the first--

DR. CLEMENS: Yes, I am, point one.

DR. HEUBI: I think it would be situations in which there clearly is evidence that, as in the case of preterm and term infants, that the physiology is virtually identical and that there wouldn't be any differences in how a preterm versus a term infant would handle a modification in the formula.

DR. GARZA: Other questions?

[No response.]

DR. GARZA: Okay. Dr. Moyer-Mileur?

DR. MOYER-MILEUR: Okay. In response to question number one, I concur that infant formulas are a special class and should be treated more like a drug than a food.

In terms of being able to generalize from one population to another, the answer is no. Preterm infants or unhealthy infants are a different population than a healthy population of term or older infants.

The ability to generalize from one product to another, the answer again is no. These products are very different in terms of composition and have nutrients that are conditionally essential for specific populations and I think we need to keep that in mind, that you cannot feed one type of product and look at one nutrient and then apply it to a different population. So no to whether or not you can combine this, as well.

Again, I believe that, overall, the ability to generalize between populations would be

an exception and not the rule and that any request to do such a thing would require individual review by an expert panel from the FDA.

DR. GARZA: Any clarifications as to rationale or content of the--

[No response.]

DR. BAKER: I have just one clarification.

DR. GARZA: Sure.

DR. BAKER: You answered the first question that--your answer was no, and then you said there may be some exceptions, is that right?

DR. MOYER-MILEUR: There is the possibility for an exception, but I don't think it should be presumed. I think it needs to be--

DR. BAKER: And the process would be through applying to the FDA?

DR. MOYER-MILEUR: Yes.

DR. GARZA: Number two?

DR. MOYER-MILEUR: Again, there really is no clear answer to this question other than to suggest that an independent board be appointed to review serious adverse events for their severity

and their frequency. I think that it is of concern that there's variability in how the reporting is currently done and that needs to be addressed, and that the post-marketing events also are at the discretion of the industry to report them to the FDA. So I think that it would be helpful if we could set up some guidelines for that. That would provide more information.

DR. GARZA: So the safety monitoring board that you are suggesting would be appointed before the study got underway or on a post-ad hoc basis as required?

DR. MOYER-MILEUR: That you would need one while the study was being performed and then also for post-marketing once the product was available.

DR. GARZA: Okay. Any questions?

[No response.]

DR. GARZA: All right. Number three?

DR. MOYER-MILEUR: And the answer to number three would be, no, that attrition rates are part of your statistical analysis, and I appreciate the large attrition that does occur with infant

studies. Wherein a term baby study may find 25 percent attrition, I can guarantee you in a preterm study it may be as high as 50 percent and those things are taken into account. But if there are differences between your treatment groups, that is something that should be looked at and divulged.

DR. GARZA: Can you amplify, how would you suggest that this be looked at? What do you mean by divulged?

DR. MOYER-MILEUR: That in your study design, you allow for a certain percentage of attrition, but in your two treatment arms, if there are differences in that rate of attrition, then there needs to be some accountability for those differences.

DR. GARZA: Any questions, additional questions?

[No response.]

DR. GARZA: We'll move to Dr. Stallings.

DR. STALLINGS: Thank you. I think it's useful to say, I think out of the process, we realize that we're all really here to build a

better formula for the infants and that we're operating, in a sense, in an environment about 20 years of almost amazing safety, so that the fact that the agency brought together both industry and the academics, these are the three groups that I think have been working well together before.

But I do believe it's time for the whole process to change and I think that's the undercurrent that we're dealing with here, so really in answer to number one, first recognize what Dr. Dickinson was presenting and I think the concept of relevance is probably a better word for us to work from than generalizability because that calls the science, I think more clearly.

I think that there should be a pre-review process rather than a post-review process so that there's actually healthy and productive interaction between the FDA and industry as they propose studies. I believe this would be helpful because industry doesn't want to go work on something for a number of years and then come and find out that they missed one piece that now we believe is there.

So I think we really are looking at an opportunity to completely revamp the system so that things would come in for the pre-review, there would be a level of understanding of the design and the intent, and I think if there were disagreements about, if you will, the relevance and the purpose of the study, that the FDA would have the opportunity to have an expert panel to work with them in sort of that conflict resolution. Obviously, the regulatory agency in the end has the right under advisement to make those decisions.

I think this would get us out of a lot of the current concerns, where I think the lack of clarity, not intent, but lack of clarity. I realize it would take a whole new way of looking at this, but I think doing it prospectively rather than in a 90-day window, in fact, after all the work has been done, the babies and families have been engaged and the money and time spent, would be productive for us all.

So I reduce that really in answer to question one that we would quickly get out of this

and, as Dr. Anderson said, we would also quickly develop a body of case studies that really would inform the agency so you wouldn't have to keep going back to your committee and inform industry about what the current process is and how well it's working and you would be able to identify the areas of uncertainty much more quickly and work on those.

So I believe that there would be a standing review panel so that this could be done quickly, because as you all know, it's hard to get us all in the room at the same time, so that the agency would be able to call on people quickly so not to delay the review of proposals and science and development.

DR. GARZA: So if you amplify a little bit, because in your preamble you said that we had an outstanding safety record. Why, then, the added review, the adage of if it isn't broken, why fix it?

DR. STALLINGS: Well, I think that--

DR. GARZA: I didn't understand the preamble and then the recommendation.

DR. STALLINGS: The answer? That's a good question. I think actually doing research, and I agree with many of the people who have already spoken, I think infant formulas are much more like drugs than they are like food and I think we all need to recognize that, so that what this is, is putting the whole system in a setting where, in fact, we are talking about clinical trials and we're managing it with that kind of appreciation of safety and design.

I also believe that I'm recognizing the level of frustration from an industry side of not having clarity of what's going on. So I think it's an opportunity to put that on the table, which will add to efficiency and getting safe products to the market, which is what the agency wants and what industry wants.

So I don't think, fortunately, in fact, Dr. Garza, that we're here today because something awful has happened, which is to all of our credits. The last time something awful happened was '79, '80, something like that, and it really did serve

as a wake-up call. But I think before something awful happens or just because we're doing the right thing, it's a chance to look at the system in a new way.

DR. GARZA: All right. Any other questions, points of clarification?

[No response.]

DR. GARZA: If not, let's go to number two.

DR. STALLINGS: Number two is the adverse event question and it goes from some of what I just said. I believe that we need to look at this very carefully and I would agree that these now are clinical trials, and in modern era work that there needs to be an independent review of adverse events.

I think there's an interesting twist to it, though, because in most pharmaceutical settings, we spend most of our time looking at serious adverse events, which are things that usually cause death or hospitalization or prolonged hospitalization, when, in fact, I think many of the

adverse events we're looking at in an infant formula setting may be things historically classified as just regular old adverse events, because they're GI, they're intolerances, they may be psycho-social.

So I think there will be a challenge to come up with a new way of looking at this and I don't have specific recommendations to offer, but I think the independent board would meet to be empaneled as a study is going on. The serious adverse events, I think would be the kinds of things they always are, which would mean you would stop the study until you were certain that your study wasn't contributing. The non-serious events, I think we have to think more about, because I think that's, in fact, the data that we would want to have.

I also agree that the post-marketing is really there for the convenience of the customer and I don't see that as a part of the safety monitoring plan as it's currently conceived, and the data on how good doctors are at reporting