their products and clinical studies together based on preliminary or pilot data before conducting, let's say, a Phase III study.

DR. GARZA: Dr. Stallings?

DR. STALLINGS: I would agree that no one should embark on studies in such a vulnerable population without a thorough review of the literature.

I would look forward to discussing a little bit more about what may publicly -- even with the caveats of what is proprietary, so that the process could be informed by other people seeing those data.

So I'm not quite sure, with the intent for COMA, what made publicly meant. Does that mean that it comes to the FDA and it becomes part of public record? I would like to see us discuss that a little bit more, bearing in mind -- because we've all seen reviews of the same data that come out with different conclusions or that one group sees gaps that another group might not.

So I think it would be interesting as to

how -- again, the goal is to get the best designed, smallest study we can to get the work done. So how might that process be improved and utilize the academic community or the regulatory community or whatever.

DR. GARZA: So your main concern is as to the extent of the transparency that that review then would be subject to.

DR. STALLINGS: Not just the transparency, but that this idea of review is always based upon the people who are doing the reviewing. If there were a way that weren't so cumbersome to have lots of input, so that we get clearer hypotheses and, yes, we should move ahead with this, it's a good question.

If this is all implied, if it's a scientific driven question more than a manufacturing question.

DR. GARZA: I'm not hearing any "let's delete it," but yet it sounds like a good principle.

DR. DWYER: I think before we go any

further, I just have a question in terms of the context. This document was produced the stationary office.

DR. GARZA: Xerox paper, actually, American now. But good point.

DR. DWYER: Perhaps it's just because I'm of Irish descent, but I did want to ask. It seems to me that looking at recommendations from another country is valuable in some respects, but it's important, for me at least, to know the context of the underlying legislation in that particular country; do they have an infant formula act like we do, do they have other things in place, protections, I would assume, do they have more, less, the same.

I don't know British regulatory law well enough to be able to see this in a context of whether this is all they have or whether we have more to begin with and we're building on this.

Could you please answer this?

DR. GARZA: Let me turn to either Beth or Chris, but add a caveat before they start. That

is, I hope none of us are viewing this as, in fact, being in any way other than a method of structuring this discussion.

We are obviously going to be adding, modifying these substantially, eliminating some, but because we don't have another structure, this is as good as any, given the suggestion.

DR. THUREEN: And much of this was based on the prior AAP guidelines, if you go back to those, from 1988. So they took much of this from American guidelines. So I think it's pretty universal, with not much adaptation.

DR. GARZA: But I want to make sure everybody understands that, because Johanna's question is very pertinent, and so that the answer comes in that context. This is just the structure of the way we move forward.

DR. YETLEY: I was just going to say these were offered simply as a strawman to help focus or help stimulate your discussion and certainly we are anticipating that you will change them as you see appropriate.

I don't know the answer to your question, Johanna, except in reading the entire document, it seemed to me that they were focusing primarily on guidelines for efficacy studies, but they also were looking, as part of that, at safety, and it seemed to me that they were guidance for investigators.

Whether or not the data was then to be used in a regulatory context or not, it wasn't clear. But it seemed to be more general guidance, guidance for nutrition studies and infant formulas primarily for efficacy purposes, but not forget safety.

But that is just an impression, having read this thing from front to back.

DR. GARZA: Dr. Hotchkiss?

DR. HOTCHKISS: My reading of this A-2 recommendation, and there is some precedent in food regulation in the U.S., that does not relate necessarily to a particular nutrient or product or clinical trial, but rather that the scientific information upon which an action is proposed should be available to the public so that the public can

see if they read the information, the history, the literature, if you will, on it in the same way.

FDA has rules, for example, similar to this in companies or private organizations that want to affirm a substance as a GRAS substance. I believe there is a rule that says that a review must be available in the public literature, the public scientific literature, so other people qualified can review the history of it.

I think that is a good idea and I think that that kind of thought at least ought to be put into anything that says we want to put more polyunsaturated fatty acids in baby food. Then there ought to be a body of literature available, not just to companies, but to the scientific and public community at large, which reviews critically that area, so people can make their own observations.

DR. GARZA: Are you saying then that that ought to be available before the agency takes any specific action? That as part of that process, those reviews or that information should be made

available to the public, allow them to comment on it, and then whatever regulation or action seems appropriate would be taken at that point, but not after the fact?

DR. HOTCHKISS: My understanding, for example, in affirming a substance is GRAS, which is available now, that the agency will not consider that affirmation unless a thorough and complete review has been published in the scientific literature and there is some discussion about -- the latest I've heard on it, at least that the ink has to be dry on it.

There's some talk that it has to have been out there for at least six months, so that people can look at the same information to see if they come to a similar conclusion or do they disagree with that conclusion.

DR. GARZA: Okay. Chris?

DR. LEWIS-TAYLOR: Just to clarify what 412 does and does not allow. Under Section 412, the submissions the manufacturers provide to the agency are proprietary. They are not revealed

until time of marketing, and then they are FOI.

So it is true that during our 90-day review process, that data is not available and the statute does not provide for it to be available.

Once the manufacturer has gone to market, the scientific evidence upon which we based our decision is available to the public. I'm not sure that informs you very well, but I just wanted you to understand what 412 was currently.

DR. HOTCHKISS: My response to that is that it seems to me if there is good reason for changing the nutrient profile in such an important product, that that information, the reason for doing that, not proprietary information about how you do it or those kinds of things, but rather the underlying science ought to be available to the community at large to make their own judgment upon.

DR. GARZA: A point of order, Chris or Beth. We can make recommendations to FDA, in fact, in suggesting it could seek legislative redress for something that, in fact, we think ought to be changed. Let's take this as an example.

Let's assume that, in fact, these reviews would only be made available after the fact, in contrast to what is done with GRAS. We could say we feel that that, for whatever reason, is inappropriate, it ought to have at least a six-month commentary period, similar to what Dr. Hotchkiss described for GRAS substances.

If, at the end of deliberations, after the three meetings, that seems reasonable, or are we constrained only within what is now permitted by law in terms of making recommendations to you?

DR. LEWIS-TAYLOR: I don't think I've ever been asked that question. My guess is there is nothing -- Linda, perhaps you can help -- but there is nothing in the advisory committee standard operating procedures that could not allow you to say, "FDA, the statute is not working as is, we think it ought to be fixed."

I know of no reason why you can't say that.

DR. GARZA: Okay.

DR. YETLEY: I agree with Chris that you

could say whatever you want.

DR. GARZA: But will they come. Great line in Shakespeare.

DR. YETLEY: It's all in the transcript. I think that what is most useful to FDA is that we have general principles that we can use within the context that we have to work within.

Then I think if you want to add recommendations for concerns you have sort of outside or to go along with those, that would be fine. But I think we do need operative working general principles that we can implement in a reasonable time frame.

DR. GARZA: That's an important addition.

DR. BAKER: I was just wondering whether both things couldn't be incorporated in this thing. I mean, couldn't -- if a company comes to you with the 90-day notice and gives you information, couldn't they also supply background scientific information that is not proprietary that could be distributed to the public at that time? So there would be a comment period. Couldn't you do both at

the same time, though?

DR. GARZA: While they're thinking.

DR. LEWIS-TAYLOR: Trying to be invisible. Again, as we've mentioned, what is useful -- what Beth has mentioned is what is useful to us is what we can use in the context, but, again, you are free to make that recommendation.

DR. GARZA: Okay. Dr. Giacoia, then we'll come back to Dr. Hotchkiss.

DR. GIACOIA: The general question seems to refer only to effectiveness and I think we cover this discussion very much if we are going to include safety in this or not.

DR. HOTCHKISS: Let me clarify this more. Again, it's in the context of this general principle A-2. I'll give you a very specific one that you can go look.

If you go look at the Food Chemical Toxicology, the publication, you'll see a number of reviews of food ingredients. What the fine print doesn't tell you is those reviews of food ingredients are really to meet this requirement of

someone, in a proprietary sense, is going to -- is in the process of filing a GRAS affirmation.

Let me give you a very specific example. If you look about two years ago, you'll find a review, a very extensive review published on polydextrose.

The real impetus for that review in all of the available scientific literature, both publicly available and often in the number of clinical studies that were not published in the scientific literature, but were reviewed as part of this, is that those clinical studies could not be used in support of that GRAS affirmation unless they appeared in the public literature.

And that is the reason that that is in there and that had nothing to do with the proprietary nature of the company who wants to put polydextrose forward. It was just an independent review of the clinical studies that support the efficacy and safety of polydextrose.

That is a very useful process.

DR. GARZA: Let me gavel this. We need to

go on to a number of others.

DR. SIGMAN-GRANT: I was just going to suggest to see page 15.

DR. GARZA: See page 15.

DR. SIGMAN-GRANT: It explains what that thought means and it's a little bit different.

DR. GARZA: We don't have to be governed by this. I think the principle of looking at making reviews public, assuring the transparency is there, is something we want to come back to as a guiding principle.

What about A-3?

DR. DWYER: Are we talking about guiding principles for efficacy, safety, or nutrition, or all three?

DR. GARZA: All three is my sense, but let me look, because you've got the whole issue of the quality factors being inclusive of all three. And that's what we're looking at, is quality factors, so that --

DR. DWYER: What I'm asking is whether these principles, this general question applies to

safety, efficacy, and nutrition, or just to safety, because some of the presentations this morning just focused on safety and I just don't know what we're trying to do.

DR. YETLEY: Quality factors refer to nutritional adequacy and safety, but it doesn't get into efficacy or claims, and you can add -- a manufacturer can add an ingredient to an infant formula without a proven benefit, provided it does not adversely affect the nutritional adequacy and safety of the overall formula product.

DR. DWYER: Then these principles that you are talking about, Dr. Garza, are principles for nutrition and safety, is that correct?

DR. GARZA: It's in response to the general question that was -- the first one that was passed out, and at least for me, it tends to be somewhat of a semantic issue, whether, for example, claiming that a formula will sustain normal growth, and we're not looking at efficacy in doing that, because if it doesn't, it becomes a safety issue.

So for some of these things, efficacy and

safety, I think, blend immediately into each other. So I don't know whether I can neatly parcel them out as you would a drug, for example, where you're looking at a specific benefit with some unrelated safety risks.

DR. LEWIS-TAYLOR: And I'm not sure it helps to unmuddy the waters, but that question of safety is with those so-called required -- that's where the safety factor is coming in.

DR. GARZA: So getting into toxicity. Does that answer that?

DR. DWYER: No. It confuses me further.

DR. GARZA: I know, but, in fact, you may be making progress, because it is confusing.

DR. DWYER: There are a lot of things that are safe, but they're not efficacious. I want to know if what I'm supposed to be looking at is whether the things are safe, period, or not. There are a lot of things that are safe, but they're --

DR. GARZA: For example, let me give you -- one that comes to mind most readily, Chris and Beth, let's assume that there is a form of folate

in a formula, perfectly safe, but it's totally unavailable. Therefore, is the claim that it's there a safety issue because the kid is going to become folate deficient even though it meets --

DR. YETLEY: Yes, exactly. The quality factor deals with the fact that the whole formula, as it is formulated and processed and marketed, provides optimum nutrition. Nothing has interfered with it providing optimum nutrition for the required nutrients and that you're not getting nutrient imbalances, such that you would get nutritional safety concerns.

So it's providing optimum nutrition. It's not creating a nutrient imbalance or a nutrient safety issue, but it's that formula as it, in its totality, provides optimum nutrition for these infants.

DR. GARZA: Dr. Russell?

DR. RUSSELL: In regard to general principle A-3, then, this clearly, to me, reads as if you were looking at efficacy and not at adequacy or safety. So it seems like if what we're

interested in is nutritional adequacy and safety most of all, first and foremost, that principle A-3 would be not one that we would be adhering to or advising about.

DR. GARZA: So you would make the distinction between efficacy and nutritional adequacy.

DR. STALLINGS: I think the crux of the matter is in this, the proxy for safety is normal growth and the proxy for not being -- for efficacy is normal growth. So we're a little caught in that.

If this were an adult study, there would be other things related to nutritional status that we would be chasing. So I don't know whether we choose to continue to split hairs, but as the question is stated, it really is about optimal nutrition as defined by normal growth.

So sooner or later, we've got to define normal growth, but we know that. But that's what we've got to come back to.

And we're not talking about efficacy. I

mean, there is not a super-normal growth. There is either normal growth or less than.

DR. CLEMENS: Allow me to comment. Let me assure that when ingredients are applied to infant formula matrix, I appreciate your comment, Beth, on the matrix of the formula, that each one of those ingredients has gone through review. It's either GRAS or it's been approved as a food additive.

So the traditional safety, as you think in terms of toxicology, those kinds of things, is not an issue. In terms of nutritional adequacy, as Dr. Russell has indicated, does the theory and practice and experience suggest there could be a nutrient interaction such that the bio availability might be compromised, that may warrant a further study, not necessarily a growth study, but perhaps some other bio indicator to show that, in fact, that nutritional adequacy is not compromised.

DR. STALLINGS: What would happen if I wanted to add Echinacea to an infant formula and I've made no nutritional claims, no health claims, literally? I just said it has echinacea, it's on

the label, and we're not aware of any compound nutrient interactions.

How does that fit in?

DR. CLEMENS: That's a fair question, Ginny. Is that a natural, a normal component of breast milk?

DR. STALLINGS: No.

DR. CLEMENS: So you have to look at what type of nutrition, that nutrition that breast milk provides and what are the physiological outcomes that breast milk provides, and that is your basis for composing and providing infant formula.

DR. STALLINGS: So we really are defined by normal term, healthy mom, breast milk composition for the whole story, no matter what.

DR. CLEMENS: And we all know that breast milk is composed of well over 200 bioactive substances and it has a very large variation. So keep that in mind. And here we have a biological variation of breast milk, where infant formula has a very narrow window to which all manufacturers adhere.

DR. GARZA: Chris?

DR. LEWIS-TAYLOR: Just to go back. In the case of echinacea, if it were to be added to infant formula, it would have to come in under 409 for a safety review for intended use. In other words, it would either have to be recognized as safe for use in infants or it would have to be approved as a food additive.

That is the threshold step. That's where you'd be looking for allergic reactions. That's where you'd be looking for any tox problems.

DR. STALLINGS: But it sounds like it wouldn't be allowable at all because it's not a part of normal human breast milk.

DR. LEWIS-TAYLOR: That's the point I'm trying to dissuade you of. It would be allowed if it was okay under 409. It can then go in. Its second test then is in the context of quality factors, does echinacea make iron unavailable. That would then be that safety question.

But if it comes through GRAS and it comes through food additive, either one, for intended

use, it can be put in infant formula.

DR. GARZA: So a principle such as the one that is listed in A-3 would be applicable only if there was going to be a health claim that was being made or some other type of claim.

DR. LEWIS-TAYLOR: I'm sorry.

DR. GARZA: Would a principle comparable to what is listed in the COMA report under A-3 be relevant either for prematures or terms only if there were specific claims being made beyond the maintenance of normal growth, however we end up defining normal growth?

DR. YETLEY: I think that the COMA report would probably have that in mind. I think that you could consider it, maybe not so much for the normal physical growth, but for some of the other nutrients that hopefully you can look at later on.

There may need to be tailored outcome measures other than normal physical growth and I think you could work on that so it came out to be more relevant.

DR. CLEMENS: We're on A-3 and bottom

line, the manufacturers follow good clinical practice. Good clinical practice says establish a hypothesis at the beginning. Done.

DR. GARZA: Dr. Dwyer, does that discussion help in terms of your concerns, to help you look a whether we're looking at safety, efficacy?

DR. DWYER: Yes.

DR. GARZA: Can you reformulate the question, as we go through the general principle, so that we'll all be clear.

DR. CLEMENS: The response, experience is that there is uncertainty with the manufacturers, either from their expert panel or outside council, or inside scientists, they frequently will contact and consult with the agency, seeking guidance in the establishment not only of the design, but also establishing and finalizing a hypothesis to which a study can be conducted.

So there is a sense and there is a real desire to work with the agency to accomplish the means by conducting good clinical practice.

DR. GARZA: Do you want to add anything?

DR. DWYER: No. I think this is very instructive. I guess perhaps process-wise, it would be easier, at least for my thinking, to go through these principles with safety in mind and then go through them again with efficacy in mind. Like adding an herb to formula may not be efficacious, but it isn't wrong, sort of like it's not unsafe.

DR. GARZA: As the discussion has progressed, what I am going to suggest is that, in fact, we come back, as Johanna has suggested. Let's focus on safety for right now. We will come back to whatever principles we end up with, and postpone any discussions that relate to general principles as to design or conducts of studies until perhaps after our second meeting, when we at least have some agreement on what the general principles should be, because then I think it would be much easier to deal with design issues.

At the present time, until we can deal with the general principles that are science based,

as to safety and efficacy, then trying to come up with general principles for the conduct and design of studies may be very difficult.

Plus, I don't think we'll have the time anyway, which is a more practical reason for trying to limit our discussion until 3:00 to a just general principles on safety, and then we'll come back and deal with safety, hopefully before 3:00, as well.

But that takes off the pressure of thinking we're going to be going through the whole list.

Let's go on to A-4 then. Any comments as to the centrality of studies of acceptability?

DR. CLEMENS: I would like to know what studies of acceptability means.

DR. GARZA: I think, at least as I understood it, from either the COMA report or the AAP report, it is whether the mothers and babies will tolerate it. When mothers smell it, do they turn green and, therefore, refuse to feed it to their babies, or fathers, for that matter, or, gee,

it doesn't seem to harm the baby, but he just refuses to drink it because it's foul. That's what I understood acceptability to mean.

DR. THUREEN: No evidence of colic or GI intolerance.

DR. GARZA: That's what I meant by green.

DR. DOWNER: So then are we saying acceptability really means palatability?

DR. THUREEN: No.

DR. GARZA: There's more than that. The other issues that were raised, actually, in both reports, you're right, is whether the baby gets colicky. That, to me, is a physiological response that shows that there is an adverse response that we just don't understand, so we say the baby is colicky. We could have that discussion later.

DR. STALLINGS: That would be data driven. I guess as a point of clarification, in acceptability studies today, what does that mean in the U.S.? That it's given to a test group and the mothers say it looks and smells okay and it doesn't make the refrigerator smell funny and the babies

consume it at adequate amounts.

Is this a sample size count driven thing?

DR. GARZA: The issue, Roger, that was raised in the reports that were sent to us was that, in fact, no firm would ever market a product that was not acceptable, because it wouldn't be marketable.

DR. CLEMENS: You're absolutely right, and thank you very much for that comment, Dr. Garza. Actually, those kinds of outcomes, Ginny, are actually assessed by every clinical trial that I've ever participated in.

So acceptability, extrusion reflects, smelliness, changes of stool patterns, frequency or appearances, all those kinds of things in terms of formula tolerance, if you will, are part of the process.

DR. STALLINGS: And so those data are presented to the FDA in this 90-day review.

DR. CLEMENS: Actually, for a study, when they introduce a new ingredient, let's say, beyond normal nutrition, if you will, those kinds of data

are, in fact, presented.

DR. GARZA: Dr. Hotchkiss?

DR. HOTCHKISS: The only concern I have is about the concept of acceptability as opposed to consumption. I think the piece of information you really want is if you reformulate it, what does that have to do on consumption.

Let me be cynical and say that I have a new ingredient for infant formula that increases individual consumption by five percent. Immediately, I sell five percent more baby formula simply because I have added this ingredient and it actually increases acceptability.

The piece of number that, if I were regulating this, I would want to know would be consumption.

DR. GARZA: There is a key phrase on that, at least the way this report phrases it in terms of functional or clinical. So that theoretically, that would fall under -- you're right and, in fact, that may have happened historically.

Dr. Russell?

DR. RUSSELL: Again, maybe I have the same problem that Johanna has. When you read functional and clinical benefit, we're supposed to substitute, in our minds, normal growth or safety, which, to you, are the same thing.

DR. GARZA: That's right.

DR. GIACOIA: Can I make a comment?

DR. GARZA: Let me see if Dr. Russell is finished. Are you done, Rob?

DR. RUSSELL: So this would be putting something else in the formula that we don't know, other than to provide for normal growth or for safety.

DR. GARZA: In addition to safety concerns, acceptability should be a criterion.

DR. RUSSELL: So if you were to put in echinacea, this would be -- we would have to make sure that this was acceptable to the infant and mother.

DR. GIACOIA: I'm afraid my pharmacologic shows up. In regard to nutrition, different from safety in regard to drugs, because I have a problem

with the definition of safety. You seem to be implying that safety is the opposite of not gaining weight, and I have problems with that.

DR. GARZA: Only in this specific sense. What I was asking when I asked the question to Beth and Chris was that if we're asked to come up with criteria or guidelines for normal physical growth, then that in itself implies inefficacious out -- or that the product is efficacious in producing that outcome.

On the other hand, at the same time, if you fail to do that, there would automatically be safety concerns that would be raised. So that's why, for me, when you're dealing with infant formula, and I realize this is a personal view, it's very difficult to disassociate safety and efficacy within the constraints of the definition of that food.

DR. GIACOIA: I think they are together, the opposite side of the coin. My difficulty is I think it's a mishmash between this document we're looking at and this question we're being asked.

DR. GARZA: Could you expand on that then?

DR. GIACOIA: I think safety is terribly important and you can think it's an area where let's assume somebody comes up with a formula that put antioxidants there, your efficacy will not be growth.

DR. GARZA: The only reason we're saying growth is that's at least a primary outcome we've been asked to look at. There will be other outcomes that, in fact, we may wish, and that's why, at the very beginning, remember, I suggested that one guiding principle for the future may be that normal growth remains necessary, but is no longer sufficient because we may, in fact, want to look at other outcomes.

But then if we do that, we get right back into this issue of the claims we would make and issues of safety and efficacy. For growth, it's pretty hard to disassociate them, but for other outcomes, they may not be and they may be irrelevant if we're only asked to look at safety and not efficacy.

That's why I thought Dr. Dwyer's question was so central. I'm not hearing that anyone is opposed to looking at acceptability as a general principle.

So let's go on to five, which is much more substantive, I think, than four, because that will present a host of challenges. Whether we look at growth or other outcomes, it still presents a number of challenges.

DR. SIGMAN-GRANT: I think one of the most challenging things is the separation of looking at outcomes versus the composition in the milk. I don't know how we deal with that.

If somebody wants to add something because it's in human milk --

DR. GARZA: You came right to the crutch of the problem, because what Dr. Clemens assumed was that, in fact, the formula would be judged only on its compositional comparison with human milk, while this general principle is looking at the outcome rather than the input. It's the output side.

Dr. Stallings?

DR. STALLINGS: I think this could be one of the more important parts of the general principles as we go through looking at them. With all of the concerns we have today, if you will, about childhood and adult obesity, with all of the questions and not many answers yet about the impact of feeding practices during the first several months, I think this will be one that we're really going to have to delve into.

And as a general principle in the U.S., it seems like that breast fed, exclusively breast fed babies, and I would just probably say instead of four to six months, just birth to six months, because that encompasses the time that I might like to see us do a few more measurements long term.

But it seems like that that, for many reasons, should be our gold standard for growth patterns and that it will lead us back to some of the questions about are we just going to look at growth as mass or are we going to be able to do body composition.

And then the second is -- which is very different from I'm adding one thing and I'm going to study it compared to the previous formula without that one thing.

I think this was well taken a number of years ago when this was established, but I think seriously considering breast fed baby patterns of growth, healthy babies, healthy moms.

Now, it gets into a whole different story for premies, but that's another principle, thinking of this from a full term point of view.

DR. GARZA: So you would add healthy term infants then.

DR. STALLINGS: Right, because I think we really don't have the science or the understanding of pre-term milk and pre-term babies and sick babies and all of that, and I would probably add looking at their growth pattern from birth to six months rather than just four to six months as a benchmark for discussion, just to start.

DR. GARZA: Any comments responsive to that?

DR. GARLICK: I don't think it actually says from four to six. It says breast fed for four to six months.

DR. STALLINGS: Sorry. You're right.

DR. GARLICK: The other point is, am I assuming correct or not that we would not judge the formulas against the composition of human milk? Does anybody seriously think that we should add it, for example, just because it's in breast milk?

DR. GARZA: No. I think the comment that Dr. Clemens made was that one would base changes on human milk, but not to match them exactly, because of bio availability. The issue here, though, is that it would be outcome in the baby rather than what you're putting in the formula.

DR. CLEMENS: That's correct.

DR. J. ANDERSON: I think one has to be careful with the language here, because I think it's all well and good to say that studies could be interpreted in light of what's understood about growth for infants that are purely breast fed, but there's obviously strong selection bias likely at

work in terms of which mothers choose to exclusively breast feed or to not breast feed.

And I know of no way to account for those differences in making these comparisons. So I would -- while it's all well and good to interpret studies in light of those data, I think using data that comes from purely breast fed is some kind of standard to which infants fed on formula should attempt to achieve, potentially raises serious issues because of the potential differences in the infants, in the mothers, and the socioeconomic background and all sorts of things.

DR. GARZA: I can help with that, because there are a number of studies now internationally showing that, in fact, where you don't have those selection biases that you have in the U.S., patterns are exactly the same.

So those selection biases appear not to influence growth behavior. They may impact on other outcomes, such as infection, but they don't seem to impact growth.

A breast fed baby in Norway that comes

from an upper income group grows very similarly in terms of pattern to the exclusively breast fed baby of educated parents in India or in Guatemala or in Kenya.

DR. J. ANDERSON: That was not what I was saying. I was saying that to -- that may, in fact, be true.

DR. GARZA: But 80 percent of the babies in these populations are all breast fed, or 90 percent. So it isn't a subset of the population that's doing it. So you don't have the same selection pressures, where only 20 percent may be doing it.

DR. HEUBI: I really firmly believe we should use breast feeding as the standard. I don't want to wave a flag here or anything like that, but I think that is a more appropriate standard for growth that we should be applying.

And Johanna's point is well taken about obesity and issues that we're dealing with. We need to be at the forefront and say this is what we consider to be the standard for growth in children,

if that's what the committee wanted to do.

DR. GARZA: I would ask the group, through. There was one part of what Dr. Stallings said that concerned me. I was involved with a review recently for WHO where certain decisions were taken because of global concerns and when we look for data for children that have been exclusively breast fed to six months, there are very, very few data sets.

We can speak and based at least on the data sets that I am aware of, there do not appear to be major differences in growth of predominant or exclusive, but if we take this literally -- when I read this, I was surprised, because I don't know where the data came from.

It's the exclusive part, using the WHO/UNICEF definition of exclusive, which is nothing, zero. There are very few studies and those studies are consistent with the fact that those patterns observed, but we should be aware, as a group, that there are not many.

The predominant part, I think there are a

lot more studies for that.

DR. STALLINGS: Thinking out of the box, if the data don't exist, we could still say that we think it is so important that that might be a place where research needs to be done or could be done as a contract or could be done, because I think there -- and, again, I am very willing to discuss and learn more about how much breast milk keeps you on that growth pattern, and, Bert, we've been with the people who know that literature.

But we really are trying to get at a pattern that reflects breast feeding as much as we could, and I don't think we should be deterred by the fact that we don't have the data today, because it may be just a part of this is work that needs to be done.

Even I think the new growth charts and most of the samples that are done, the samples of children that are in those data in birth to four months or birth to six months are extraordinarily small.

So I think we go -- well, let's use

national standards. Certainly, the people in industry and many of us around the table know that you're looking at 20 or 30 or 40 kids. So it may be time simply to have data collected to serve this very important purpose and it would be contemporary and it serve us for ten years or until it needed to be redone.

DR. CLEMENS: It's a great idea, looking at breast fed kids, and I really, in principal, support that. It's a practical matter of trying to get moms to participate in studies at the front end.

Also, to look at, to a number of comments made around the table, what are the appropriate biological outcomes and do moms want to submit their breast fed infants to those biological outcomes.

It's very difficult to recruit for those things, looking at immunological factors, allergies, pick one, it doesn't make any difference.

Moms' behavior -- to your comment, Bert.

Behavior of breast fed moms is much different and perception is much different in terms of allergies, perception of different types of infections, whether your child is breast fed or if a child is formula fed, versus real clinical evidence of presentation of pathologies.

DR. STALLINGS: The only thing that counters, because it's hard doesn't mean we shouldn't do it. For those of us who do clinical research in disease states in children and in healthy children, I know it's hard.

But I think if we believe it's the right thing, there are ways of doing it. In fact, a growth study might not require the blood samples and the urine samples and the stool samples that I require in a lot of the other studies.

We really are talking about growth and I believe that I could do informed consent with families and tell them why it's important and ask them to volunteer for six months of growth measurements, especially if I went to their home and did it in a convenient time with great

equipment and nice people.

Yeah, it would be hard, but it's a lot easier than some of the other work. So I think we're on the same wavelength, but I just -- I don't want us to shy away from what we might really need to do.

DR. CLEMENS: I think everyone, all the manufacturer representatives today have those kinds of data. The question might be do you change the plot from NCHA standards versus breast fed, exclusive breast fed kids for, say, six months. Do you go contact Kate Dewey, pull all the WHO data in and say we can plot those data, have the people plot them for us, and then say these are the growth charts we want to follow.

Then all the kids that are breast fed or formula fed clearly will fall in the 80th to 100th percentile, if not above, and are we going to say that those kids are unhealthy, maybe because they're formula fed versus kids who are breast fed?

DR. STALLINGS: No.

DR. CLEMENS: Thank you.

DR. BAKER: I'd just like to make one comment about Ginny's thing about not having the data. I think the reason we don't have the data about exclusively breast fed babies is that that's not the practice in the world. There is no population in the world that exclusively breast feeds for six months. Four months, yes, but not up to six months.

So it's going to be difficult, unless you get a special group of kids whose parents are willing to do that, to get that kind of data.

DR. GARZA: Let me give the group some information that you may find useful. Again, I am participating in a study that is being carried out by WHO in six different countries, attempting to recruit 300 infants, follow them for two years, and trying to sustain lactation for at least four months, but ideally six, with exclusive and with continued breast feeding to 12 months.

When this study was started three or four years ago, the comment that Robert just made, Dr. Baker, was absolutely everybody's assumption.

We, therefore, proceeded to incorporate very strong breast feeding support. And notice I said support, not promotion, because women, at that point, don't need cheering squads. They, in fact, need some support in terms of how do I manage this clinical problem or another, and rates, success rates of 70 percent were achieved, among working women, because many of these women were working.

So the idea that, in fact, this is not possible as a biological phenomena or as a mantra, if, in fact, you're willing to put in the resources to support it, and there is a big "if," you can do it.

And those data, unfortunately, won't be complete -- those studies won't be completed for another year and a half or two years, but there will be a U.S. sample of at least a 100 children, together with -- and that was because the recruitment levels were lower in a planned way, because their success rate was going to be so high.

In other countries, that level of confidence was not there. They recruited 300 and

we're going to end up with over 200 infants. Exclusively breast fed for at least four, a great proportion for six, with continued breast feeding for 12. So it is possible.

DR. CLEMENS: It may well be part of the question here is breast fed kids in, say, Hungary and the former Soviet Union, are those applicable to the U.S. population. Are the biological outcomes supposed to be the same?

DR. GARZA: When we've looked at preliminary data, and the studies are not completed, the only outcome, for the reasons that I think you alluded to, we'll be able to get blood samples, it was primarily a growth study, with growth being measured 24 times during the first two years.

The patterns of growth were exactly -- appear to be, at least for right now, and they may turn out differently when it's all over, appear to be very, very similar from Ghana to Oman to India to Norway, the U.S.

So it's the whole range of ethnic

geographic populations.

DR. DWYER: I think this is a different agenda than the one for this meeting.

DR. GARZA: I was responding to --

DR. DWYER: And we need to get back to --

DR. GARZA: To the growth issue.

DR. DWYER: I also don't see anything in the Academy of Pediatrics June '98 statement that talks about this.

DR. GARZA: No. You're absolutely right, and, in fact, that's why I thought that A-5 was key, because we're going to do it. It's a brand new principle and you ought to be aware of as much information as you can have.

DR. DWYER: I think we should hold it in abeyance for a whole.

DR. GARZA: In terms of discussion or just eliminate it?

DR. DWYER: Until the data is published in the peer review literature, I don't think there is any need to talk about it.

DR. GARZA: Any comments?

DR. STALLINGS: I'd like to continue with something we discussed further in the future, but I think we've aired it enough today.

DR. GARZA: Any other comments? We have one that says no, we ought to eliminate it, and one that says no, let's keep it further discussion. I don't get a good sense from the group how you would like to go.

Is there anyone that does not want to keep it, other than Johanna?

DR. CLEMENS: I support Johanna's position. This is not part of the charge today. Right now, we don't have those data. We can move on to look at clinical issues.

DR. STALLINGS: If the whole issue is comparison to growth and the growth data that's been used are generally the incremental growth data from the last 30 or 40 years, which most of us know all of their strengths and their limitations, then I think talking about what growth standards we are going to use is pertinent.

Breast feeding may not be the right one.

The charge may be that we need a new sample or the issue goes to one of the others about control groups. There are lots of ways of dealing with this.

But if your primary outcome measure is growth, we've got to have a consensus of what that goal standard for growth would be.

DR. SIGMAN-GRANT: If we're using breast milk as a primary standard for infant feeding, then I think the growth of breast fed infants has a role here, a place here as a primary standard.

DR. GARZA: Let's go ahead and at least keep it further discussion and we will then challenge both Roger and Johanna and the rest of the group that feels differently, that, in fact, we look at the data and then try to come up with what the appropriate reference should be in terms of looking at normal growth.

All right. What about number A-6, which really speaks of the same issue? Not growth, but other behavioral outcomes that are much more difficult to assess.

DR. CLEMENS: Those kinds of studies, pre-clinical evaluation of potential components are conducted by each one of the manufacturers represented today and those data from those studies are, in fact, presented to the FDA in the process of pre-market notification.

There is a good history that the various manufacturers work very cooperatively, trying to introduce new concepts and renovation, innovation of infant formula, and it goes to the submission of data from good clinical studies.

And I dare to say that people around this table have participated in those kinds of pre-clinical studies.

DR. GARZA: So you feel the reference data sets are available, so that there's no need to develop them. Is that the point you're making for A-6?

DR. CLEMENS: Absolutely. The manufacturers have done an excellent job of evaluating these in terms of safety, potential efficacy. The issues have been brought to this

table.

DR. GARZA: So the only thing we don't have are growth. We have the other outcomes.

DR. CLEMENS: Actually, some of the pre-clinical studies, they may have a sense of where growth is going to go, but the design or the choice of subjects, if you will, or the primates were animal models.

They're not going to initiate a clinical study if there is anything that would suggest that there would be any interference from a nutritional quality perspective or would inhibit growth.

Hence, when Dr. Lien presented his data today, he showed here is what happens when we mix these fatty acids compared to breast fed kids at certain times. This is what happens when we feed kids this profiles of fatty acids from time zero to time Y, showing the velocities comparable.

So then we have a good sense of what is going to happen to those parameters before actually doing absolute long term growth studies.

DR. GARZA: Any other comments? Are there

other general principles then that are not included here that we ought to think about?

DR. DWYER: What about reasonable cost and time? Reasonable time and cost.

DR. GARZA: Reasonable cost and time for the mother for preparation?

DR. DWYER: It would seem to me that you would want some kind of criteria about those two things, wouldn't you?

DR. GARZA: I'm sorry. It was for showing safety or for in their actual use by the parents, when you say time and cost? I wasn't sure.

DR. DWYER: Showing safety.

DR. GARZA: Showing safety.

DR. CLEMENS: Again, GRAS and pre-notification and then safety assessment, before it even gets to this stage, and in pre-clinical trials, potential clinical outcomes are assessed in those models.

So you have really very good sense before you even initiate a clinical trial what those outcomes might be in terms of safety, as well as

potential efficacy.

So in my mind, it becomes somewhat moot. You've got a certainty, there's a really good sense of certainty, not absolute, but a good sense of certainty that when you go to clinical, you're going to have a reasonable outcome.

DR. STALLINGS: And I'm sure I don't know as much about it, but the sample sizes and the power calculations and things like that, because I've often worried, in our current environment, where changes come from one company or the other at a time, there are limited resources and it's very focused work.

I have been concerned sometimes about the sample sizes for the secondary and tertiary concerns, separate from growth or whatever, whatever really needed to be done to be able to take it to FDA for approval.

So you are sounding extremely confident in that scenario, having studied enough babies long enough to pick up virtually everything.

DR. CLEMENS: I have worked with in-house

statisticians. I've worked with consulting statisticians. I've worked with numerous universities in designing good clinical trials.

In every situation, we've tried very hard to address all the points that have been brought around this table, potential outcomes, adverse events, attrition. So those issues are pre-addressed before the clinical study is even put on the table.

DR. GARZA: Dr. Hotchkiss?

DR. HOTCHKISS: I would like to ask Dr. Taylor just for a point of information. How many infant food manufacturers are there regulated by FDA, what's the number? We have heard something like five in this meeting. Does that comprise some of the industry or not? Infant formula.

DR. LEWIS-TAYLOR: Relative to infant formula manufacturers, not infant food manufacturers, they are a small industry in the sense of five or six companies. So you have heard from most.

DR. STALLINGS: Just not to get in a

respectful banter, but I continue to have concerns about the unequal attrition rates and the sample sizes at the end of the studies and that sort of thing. So I think that's something we need to keep talking about.

DR. GARZA: We're going to come back to those issues after 3:00 today. In terms of general principles, though, one issue that we sort of have discussed, but not really come to terms with, and that is if you're looking at physical growth, is it attained growth or is it pattern, given either as velocity or growth pattern, that should be looked at?

If we look at the AAP report, it was weight gain, I think it was three months, maybe six months. Obviously, there's a lot of things that happen between zero and three months.

Is the pattern of growth something we ought to pay more attention to, as a general principle, or is the general principle looking at only attained milestone sufficient?

DR. CLEMENS: You've raised an excellent

point, and so we can move on. But clearly, if you look at total growth patterns, kids channel out, you want to look at what is going on, clearly.

But if you look at the overall data, you plot the growth patterns, like everyone in this room has done, you find, with very, very few exceptions, kids follow what they are genetically predisposed to follow based on that composition.

In all the hundreds of kids that I have managed through the years, over 20 years of experience, I've never seen a kid go like this and fall out, never.

DR. GARZA: Dr. Stallings?

DR. STALLINGS: In most of the studies done for this, I don't think the genetic potential for growth is even assessed, because the data to do that would require the biological parental heights, and that's not a part of the database.

So I think, in general, what you're doing is saying that they're growing around the usual patterns if you plot them on the growth chart.

So we're not quite to genetic potential

questions and that would be a different story.

DR. CLEMENS: You're right. I must admit, though, I have tracked some small for height parents, if you will, small for age parents, those who are somewhat not vertically challenged, and appropriately monitored those kids.

DR. HEUBI: Roger, I'm going to invite you to Cincinnati to see some of these kids that are not growing, which then raises another issue that came up this morning in terms of the healthfulness of the population that is being assessed.

It sort of borders on a design issue, or is it a general principle that we ought to think about that isn't addressed by these six. Dr. Stallings was the first to raise the issue.

DR. STALLINGS: I think in full-term infants, we are expecting that the babies that are enrolled are enrolled at a time there are really very serious exclusion criteria, that you're expecting those to truly be normal healthy babies, and I'm sure, in the design part of the attrition, there's the few kids who get something that you

didn't expect when you met them at two days of age that you find out a little later.

I think it's a very complex issue, as I brought up this morning, what we really should be doing with pre-term infants, because we really are designing formulas to take care of very sick babies, and I look forward to discussion of an inclusion and exclusion kind of approach to that, in the same way we were doing.

But I would imagine we have consensus about term babies who are being studied really are healthy babies, and that you build in design if you find out someone had an unexpected congenital disease that we find out about 21 days later, they may stay in your intent to treat analysis, but we know that those are different babies, the heart disease shows up.

DR. GARZA: Dr. Dwyer?

DR. DWYER: Just an observation. I've been involved in several longitudinal growth studies, but the most recent ones have been ones that are in clinical settings, not ones where NICHD

or somebody else paid for the study to be done.

I'm a little confused and need some guidance from the rest of the committee on what we're talking about, because when I think of the clinical studies that I have been involved in most recently, there's a great -- these are not studies of infant formula, just studies of kids growing.

Our biggest problem is we don't have heights, we don't have weights. I think all of you who work clinically know that if you go into a clinic, usually there isn't anything or the kid's weight is ten pounds more two weeks later than it was before.

The state-of-the-art out in the places where these studies are being done is not very good, in my experience. So what is the level, what is the reasonable standard for doing these studies.

These are not longitudinal cohort growth studies.

DR. STALLINGS: I think if you are doing a research design study that adheres to good clinical practice, which means that you have trained

personnel doing those studies and you're not relying on the clinician to collect your data, that's -- no offense, but they're too busy to keep --

DR. GARZA: Step on a few toes around the table.

DR. DWYER: You've made the point.

DR. STALLINGS: I think you're talking about having a protocol, training personnel, and having standardized equipment. It's no longer acceptable to be doing our studies on weight scales that aren't digital. We should not be doing growth studies without appropriate leg boards.

You're providing a unique source for the whole nation.

DR. GARZA: We're sort of moving into conduct. Are there general principles, though, that -- again, taking a look at these six, we'll be breaking in about five minutes for -- yes?

DR. DENNE: One other thing. We kind of danced around it. I heard some consensus that we really ought to consider body composition. The

changes in body composition ought to be measured in any nutritional assessment.

I understand the barriers there. It's difficult. I actually think the technology is advanced to a point where we can actually interpret that within populations.

But in any case, I think it's an important principle that we ought to continue to discuss probably.

DR. GARZA: So the principle being going beyond just attain mass.

DR. DENNE: Absolutely.

DR. GARZA: All right. Any others? All right. Again, a very useful discussion. We said we're going to come back to efficacy. We're looking primarily at safety.

Would you change any of this, looking through an efficacy lense?

DR. STALLINGS: Clarify, Bert. Efficacy there is something other than growth. It's adding a component for another outcome, thinking of it, if you will, more in a drug model or where we're

adding this for a --

DR. GARZA: Or let's use the echinacea example again, that, in fact, one is going to be doing this because you expect that the kid is going to have less colds. Obviously, that's an efficacy issue then.

DR. CLEMENS: You could dwell on echinacea, but I won't let you.

DR. GARZA: I'm sorry. I just picked it because --

DR. CLEMENS: It's really okay.

DR. STALLINGS: I picked something that would have little likelihood of happening in the near future.

DR. CLEMENS: That's a good choice. I'd like to turn your attention perhaps to look at taurine. It's in the statutes in just about every country in the world. Is it really efficacious to put it into formula?

DR. STALLINGS: What's the outcome? In walking through that, what's the outcome?

DR. CLEMENS: There aren't any clinical

data to say it's absolutely required.

DR. STALLINGS: For?

DR. CLEMENS: For, pick one.

DR. STALLINGS: Growth?

DR. CLEMENS: For growth, not required for growth, it's not required for neuro development, it's not required for bile acid simulation. There are no data whatsoever in terms of humans, babies, that it's absolutely required.

DR. GARZA: In coming back to then number A-3, that, in fact, if one were to apply a principle that says if you're going to add something to formula, i.e., taurine, that, in fact, that should be hypothesis driven.

DR. CLEMENS: Hypothesis driven, with a functional physiological, clinically relevant outcome. If it's not clinically relevant, if it's only statistically significant, it has no merit. It should have a physiological benefit to the child and whatever that outcome might be.

DR. STALLINGS: And breast milk.

DR. CLEMENS: Do we have enough data on

breast milk fed kids to look at beyond normal nutrition for tomorrow? The answer is no. We barely have growth data. We clearly don't have sufficient data for, say, immunological responses or allergies.

Clearly, we have morbidity and mortality data, but we do have, say, the total span of immunological response.

DR. GARZA: I'm confused, because I think when we looked at A-6, you said there was no need for additional reference data for other outcomes for breast fed infants, that we had all the reference data that was needed.

DR. CLEMENS: We don't have enough data. So that would actually become a black hole.

DR. GARZA: So you would say should be developed.

DR. CLEMENS: If we want breast fed children, the answer is that has to be developed, but we're not there. We have a lot of data on kids who are term babies, we have data on kids who are from 32 weeks on up, but we don't have the data on

some breast fed kids.

And I would submit to you that the infant formula industry will not support those kinds of studies unless it's pertinent to their particular product.

DR. GARZA: That's why I was looking at the should be developed. Obviously, that would be hypothesis driven, but I interpreted your comments that they were already there, and I didn't want to -- I was going to ask you in private where they were.

DR. CLEMENS: I'll tell you publicly.

DR. GARZA: All right. Efficacy then. Are they pretty much the same? Johanna, you raised the issue. If we first looked through a safety lense, are there things that you would suggest the group rethink in terms of if we're looking through an efficacy lense?

DR. DWYER: I'm sorry. I'm still struggling about what the law is here, what is -- this is a regulatory agency. What is it that our charge is in terms of this?

DR. GARZA: So the question to Chris or Beth.

DR. LEWIS-TAYLOR: As I read 412, Johanna, the issue of efficacy is not, I think, the way you are referring to it, which is proof that every ingredient in there is added for a purpose.

Rather, the efficaciousness comes under the 412 assurances that the infant grows because the essential or required nutrients are there.

So it would provide the growth, because if one nutrient or another component that was added is prohibiting a nutrient from being properly absorbed, the baby won't grow, and that's considered unsafe.

So I think it is important to unhook from kind of the classic toxicological view of safety, which is taken care of in 409 as a threshold issue, and move instead to what Congress, in its wisdom, called quality factors, which was all about providing growth for infants based on the assumption that you were talking about those nutrients that are tabled or listed by FDA as

having to be there.

That's the safety/efficacy that's on the table and the efficacy is growth.

DR. GARZA: Chris, to follow up with that, is it also in the language that, in fact, as science progresses, that, in fact, one might want to define what growth means?

DR. LEWIS-TAYLOR: Exactly.

DR. GARZA: So that's what I think we have to keep in mind. That's why --

DR. LEWIS-TAYLOR: What Congress said is that they anticipate science will evolve and other quality factors will become obvious.

DR. GARZA: So that's the dilemma. That's not a dilemma, but I think a confusing issue for us in terms of safety and efficacy, because increasingly I think it's going to present us with the same challenges that looking at growth does, that they become either two sides of the same coin or increasingly inextricable, because if you don't do something, is it unsafe if you don't see the outcome.

DR. LEWIS-TAYLOR: And I think examples that have been given in terms of besides normal growth are things like immune function, those types of things have been added as potential quality factors to be measured.

Now, as we sit, the quality factor is normal physical growth and the efficacy that is on the table for 412 is normal physical growth.

DR. DWYER: If I went down this list, let me just say that I like my formula pink instead of white, and I just put a little vegetable dye into that, not enough to do any harm, and the growth was fine.

I'm not sure all of these standards would apply. What I'm thinking of is the efficacy of putting this little food dye in, which is a -- I don't think one would apply, would it?

DR. GARZA: If we go back to Roger's, you would have to show that, in fact, it was normally in human milk or have a reason, a functional reason for wanting to add the dye. We're back to the echinacea example.

DR. CLEMENS: Breast milk is not pink, typically.

DR. DWYER: What if I eat beets?

DR. CLEMENS: A lot of beets and bubble gum, red 40. So we're not going to make it pink. Clearly, the standard, whether it's growth or composition, but bottom line is performance and how do you want to assess performance.

Is it only growth? No, it's not only growth. Clearly, a lot of the other physiological and clinical outcomes we want to be assessing in the near future.

DR. GARZA: And on that happy note --

DR. YETLEY: Can we make one more comment?

DR. GARZA: Please.

DR. YETLEY: Trying to help Johanna. If you wanted to add a red dye, that's a food additive issue. Now, if there was a reason to believe that that red dye would interfere or affect the optimum nutritional qualities of that formula, if that red dye is high in iodine and adding that dye might somehow interfere or augment the vitamin iodine

activity of that formula, then that would kick in this 412, this quality factor discussion.

But if it's simply a food functionality, it would not be anticipated to affect the nutritional quality of that formula.

DR. DWYER: Beet juice.

DR. YETLEY: Then it would. But if it's red dye and it might interfere or affect the safety or the adequacy of the iodine content of that formula and the nutritional functions of iodine, then it becomes an issue for the 412, the quality factor discussions that you're having now.

DR. GARZA: It's 3:00. Let's be back by 3:15. Then we will proceed on to have a general discussion of the six questions. We will, if we have time before the end of tomorrow, come back to these general principles, so we can perhaps structure an agenda, at least the outline of an agenda for the follow-up meeting.

[Recess.]

DR. GARZA: Please take your seats and we'll get started. You were handed, during the

lunch break or right before lunch, the reformulated general questions. If you will please take them, what we would like to do is go through today's questions.

Question number one, which was a composite of A, B, and C, and then question two, and question three.

We will be spending the remainder of today and tomorrow on these three questions. As I suggested earlier, what we may want to do is try to cover, at least see how far we can get with all three questions, perhaps spending about 30-40 minutes on each for the remainder of today, and then coming back tomorrow and revisiting them and then at the end of that second revisit, then try to come to a consensus of where we will take votes, and then the advice, as I understand, is taken seriously by FDA in formulating whatever regulations they are required to.

With that, let's start then on today's question number one. Is it appropriate to generalize the results from clinical studies not

done under intended conditions of use to different conditions of use, and then you have the three conditions under that, with the example of pre-term to term or healthy to diseased.

Now, just to make sure everybody is still on the same pattern or on the same wavelength, same page, the discussion we just had applies to general principles then that we will be returning to in subsequent meetings.

It was intended to spend at least an hour and a half to help the staff organize the agendas for those two meetings, not to bring us to any conclusion.

We now are returning to the focus of this morning's discussion, which were these questions, for which we do have to come to some conclusion, some definitive stance for use by FDA.

So let's then shift gears and talk about question one and spend about 30 minutes on question one, maybe a little bit less, if we can get away with 20, and really be out of here by 4:30, as the agenda says we should be.

DR. MONTVILLE: From what I heard this morning, I think the answer is a definitive maybe. Perhaps the industry should be allowed to rely on other clinical studies with supporting arguments on why this is appropriate, because we've agreed, pre-term to full term, that's probably going to be all right most of the time.

I'm sorry. Vice versa. Pre-term to full term will be okay. Full term to pre-term, that's really, really sketchy.

So isn't there some cases, yes, some cases, no, and they should be handled on a case by case basis.

DR. GARZA: So you're addressing the one population to another. Perhaps we should start there.

DR. MONTVILLE: Or one product to another or a combination of the above.

DR. GARZA: Okay. And what criteria would you suggest be used to help condition the maybe? Certainly, if there are no major nutritional changes, like the example we heard this morning of

the fat protein blends that were used throughout a variety of products, they are nutritionally the same in all of those products.

If there is a question on whether it's a major or a minor, then the FDA might ask for more data. If the populations are very different or one could think of physiological differences, such as the difference between pre-term or full term, the FDA may choose to reject that.

DR. MONTVILLE: So that if the measure then that -- if whatever product was measured in pre-terms and they were able to support normal growth, that in itself would be sufficient, given the fact that they had a history then with all the other ingredients.

DR. GARZA: Any others?

DR. DENNE: I might have a somewhat different view. The question is why should a pre-term infant be a model for a term infant. Why should an inherently unhealthy, physiologically and metabolically distinct population, who grows very differently, be a model for a healthy term infant?

And I think that pre-term data is very useful in supporting studies for term infants, but I don't think it can ever be actually used exclusively to change term formulas.

DR. GARZA: Could you elaborate a little bit more? Is it just because of the physiological differences between the two groups that would concern you?

DR. DENNE: Yes. I think that there are a whole variety of issues. I think there are physiological differences, there are nutritional requirement differences, there are growth differences, and we're even talking about study design differences that I think we talked about today, which is at least for the first part of pre-term infant studies, they are done under highly controlled conditions, where intakes may not be terribly variable.

Term infants, on the other hand, intakes can be quite variable. So you may miss either toxicities on the upper hand or inadequacies on the lower hand that you will never pick up in a pre-

term population study like that.

DR. GARZA: Okay. Dr. Garlick?

DR. GARLICK: Is there a possibility of risk of a toxicity in the term infants if they're based on the pre-term? An example is the protein intake, which must be very high in the pre-term to support the enormous rate of growth.

In term infants, growing a lot slower, that would be greatly exceeding their requirement and maybe reaching a toxic level, because I don't know whether there's any information on what are toxic levels in term infants, but I know I haven't found any when I've looked at them. The data are in pre-term infants.

DR. GARZA: You mean toxic level for the term?

DR. GARLICK: For protein.

DR. GARZA: What would you use as an outcome for toxic level for protein?

DR. GARLICK: I don't think there's any data.

DR. GARZA: What would you measure? Would

it be urea levels or would it be ammonia level in the term infant?

DR. GARLICK: No urea. I think probably ammonia levels, but the effects of high protein, if they're there, are likely to be neurological damage. So neuro toxicity.

DR. GARZA: So you would look at neuro toxicity then. If you have any particular measures in mind that would be particularly useful in that?

DR. GARLICK: None personally. I don't know.

DR. CLEMENS: We're not looking at feeding a pre-term formula to term kids. We're looking at the useful data that may come out of a pre-clinical -- a study from a pre-term evaluation.

So in this case, Dr. Lien had presented this morning data on LC PUFAs. He showed that relative to breast fed and term babies or pre-term babies, how that can normalize out and was safe, efficacious, and mimicked, in this particular case, breast feeding in terms of the plasma ratios of DHA and arachidonic acid.

So clearly the issues of overloading Vitamin A, protein, osmotic pressure, those things, those issues, you would never feed a product designed for pre-term kids to term kids.

What you want to do is take that population which you -- physiologically, to your comment, that's appropriate to study -- pick a component -- that would provide sufficient or at least introductory data to justify the composition in a term formula.

DR. GARLICK: So you are, therefore, going to completely alter the composition when going from pre-term to the term, which I think is a perfectly good reason why it should be adequately tested again in the term infant.

DR. CLEMENS: You gain a great deal of safety and efficacy data when you're looking at pre-term kids, when it's a physiologically and medically indicated and justified ethically, and, also, for term, looking at the product matrix, which Dr. Lien addressed briefly.

Again, you gain a great deal of insight on

the stability issues and other factors, nutrient-nutrient interactions using a pre-term formula versus a term formula, which you would not gain if you used strictly on a term basis.

DR. GARZA: And I forgot, I apologize. I was asked to identify these people I had forgotten, the non-voting members of the committee. So Dr. Garlick is here as an expert. Dr. Giacoia is here from the NIH. Dr. Clemens is here as an industry representative. Everybody else, I think, is either on the parent committee or on the ad hoc committee.

MS. HAYDEN: And we also have two industry representatives that may come in, but may not vote.

DR. GARZA: And they are Dr. Dickinson.

MS. HAYDEN: Dr. Dickinson and Mr. Scholz.

DR. GARZA: So we have three industry representatives.

MS. HAYDEN: Including Dr. Clemens.

DR. GARZA: Including Dr. Clemens. I'm sorry. We have those other two and they are non-voting. All right.

DR. STALLINGS: As a point of

clarification, if you were doing this, if you were taking something that had been well studied in a premature setting and using that, when it comes to the FDA, would there also be studies on term infants to supplements, that would be evaluated at the same time or could that review come purely out of the experience in the pre-term setting?

DR. GARZA: That's the question.

DR. YETLEY: That's the question.

DR. GARZA: Now, do you want to answer the question, Dr. Stallings? You get to answer the question. Beth gets to ask them and you get to answer. That's the drill.

DR. YETLEY: That is exactly the question, Virginia. If the clinical study that comes in as part of the package, and the package probably has a lot of other information, if the product that is intended to be marketed is a term product for a term infant population, but the only clinical study or the major clinical study is a pre-term formula in a pre-term population, or vice versa, that is the question, how do we deal with generalizability

of those results to the intended marketing use.

DR. STALLINGS: Is there a minimum number of studies required for review?

DR. YETLEY: No.

DR. STALLINGS: So one pre-clinical study, properly designed, could be all that we need.

DR. GARZA: You said pre-clinical.

DR. STALLINGS: In the 90-day review, in the pre-marketing study, long term.

DR. YETLEY: No. There is no prescription as to numbers or types of studies.

DR. CLEMENS: And the pre-market notification process, there is not a checklist. It's a courtesy. It is an attempt to work with the agency on these are the data, these are the safety data, if you will, if they're warranted, these are the growth data, if they're justified.

The objective for these kinds of studies, does it scientifically make sense, is it medically warranted, and is it ethically justified, bottom line.

If it's physiologically appropriate, the

answer is to say those data may be used. If it's not physiologically appropriate, to Dr. Montville's comment, then you use, in this case, a term infant.

DR. GARZA: Beth or Chris, Roger just used a phrase that would be very useful, I think, for me, possibly for others, that it's a courtesy for industry then to give you that information.

When is it not a courtesy? What's required? What's not?

DR. CLEMENS: Actually, required.

DR. LEWIS-TAYLOR: He wishes to amend his commend.

DR. CLEMENS: I wish to amend my comment. We're required by statute to give a -- manufacturers are required by statute to give a 90-day notice.

DR. GARZA: I thought so. I thought we better clarify that.

DR. CLEMENS: Also, they can find reason to object and still, as I think Dr. Yetley had indicated, they can certainly go to market, but they would be foolish to do so, I would think.

Wouldn't you think?

DR. GARZA: Is any major modification or new formula -- so that the question then relates to major modification or new formulas.

DR. LEWIS-TAYLOR: I think the phrase major change.

DR. GARZA: Major change. All right. Dr. Hotchkiss?

DR. HOTCHKISS: I think the reason that this particular question is difficult to answer is because it's in the abstract.

Given a specific formula, a specific pre-term study, if it were passed around this group and studied by this group, then I think that an answer could probably be achieved of whether you need to do a term study or not.

On the other hand, a different study might be passed around the group and it might be a different conclusion. In other words, that the answer to this question depends on the particulars of the issue.

This is not unique in regulation of food

and drugs. Typically or in other cases, a provision is made that a panel of, I think the wording is something like a panel of experts, through training and experience, qualified to do this, must do -- and so forth, and as part of the submission, then that opinion is put forth, not binding to the agency, but rather says that we've gone out to people who we think know something about it, who are independent of the question, and they agree that we either need to do a further study or we don't need to do a study.

Some provision like that seems to me to be the only really reasonable answer to this, because it depends.

DR. GARZA: Is that true or -- let me ask the group. Am I correct in assuming that everyone feels comfortable with saying no, if a term formula or, rather, a formula is tested in term infants, but then would be used in pre-term infants, that, in fact, general consensus that in that case, it's no.

In fact, in going from pre-term to term,

then we have the somewhat -- one view that says the definite maybe or a decision tree that would take into account the sorts of issues that Dr. Denne, that Scott raised, and perhaps that the best way to respond to that question would be through some review process, be it internal or external, but it would almost have to be on a case by case basis.

DR. BAKER: Just for my own clarification. Obviously, in the best possible world, you would do a term study and you would do a pre-term study. So what exactly is the impetus to use the pre-term data? Is it because it's easier to do the studies in the pre-term or is it because they're already done? What is the impetus for not doing it in a term population?

DR. CLEMENS: In an appropriate pre-term population, you can get much more data in terms of -- look at growth, for example. You have kids undergoing the immunological process of development. You can get different phases of neurological development.

So you can get a different set of data

that might be a greater indicator or better indicator of adequacy, nutritional adequacy.

DR. GARZA: But Dr. Baker's question is, is that because of convenient sampling or because of physiology.

DR. CLEMENS: Because of physiology. Pre-term kids are very, very difficult to recruit.

DR. GARZA: You said pre-term kids are very difficult to recruit?

DR. CLEMENS: Yes.

DR. GARZA: Pre-term kids.

DR. CLEMENS: And term kids are equally difficult to recruit. Let me tell you.

DR. GARZA: I'm confused. Is it physiology or is it convenience or both?

DR. CLEMENS: It's a combination, there's no question, but physiology is what we want to look at.

DR. GARZA: Dr. Stallings, and then we'll go down this way.

DR. STALLINGS: A couple of issues. I think part of -- you know, in full disclosure and

honesty, if I was having this discussion, at least there is one important example where the studies have been done in pre-terms, and it would cost a lot more money and take a lot more time to do comparable studies in full term babies.

I think we all appreciate we don't want to waste children to studies or money if we don't have to. So I would differ that I don't think it's the advantageous physiology of pre-term infants or the way to study term babies.

But the reason I raise my hand is I keep trying to couch this in, as a pediatrician, there are healthy kids and there are unhealthy kids, and when I've spent my time working on nutrition and growth in unhealthy kids, it still seems fundamentally not a good -- if money and time were not the issues, if it weren't those issues, that I would never do a study in an unhealthy group of people, which I contend the little premie is, except for maybe that last week or two of prematurity when they're pretty close to term.

I would never choose to do a scientific

study in an unhealthy group to generalize to a healthy group. So I think that's one of the fundamental things that I keep coming back to.

So I think the challenges in our current environment, how do we balance those things, because I would much rather have data on a new compound in term babies that it's intended to use.

It's a different matrix, it's a different formula, it's regulated differently by the baby and the mother than when they're in my nursery, and I give them a 100 cc's of this and this much TPN and this much by mouth by nursing and after 20 minutes, put it down the NG tube.

It's a whole different experimental environment. So I still struggle a little bit with -- so I'm a little less than always a maybe. I think that there could be exception to when it's the right thing to do for the right reasons, but the idea of having -- we have to, I think, go to individual evaluation or else the answer is no.

DR. GARZA: So the default is no unless there is justification.

DR. STALLINGS: Right. Because I think we certainly can't sit here and imagine everything that might come up that would be important both to industry and the babies.

DR. GARZA: All right.

DR. RUSSELL: A somewhat different view maybe. In listening to this, I seem to think that the answer is it depends. But think about maybe how we could be most helpful, and that is to possibly come up with a frame work to help FDA decide, by giving weight to factors of how different the physiology is population to population that you are studying versus marketing to, and how different the product is and in what factors, whereby you could come up with a matrix to judge whether or not a study needed to be done or whether or not more study didn't need to be done.

That is, it could be generalized.

DR. GARZA: So are you suggesting that we try to develop that matrix before tomorrow, or make the recommendation to develop a matrix that would take composition and selective physiological

outcomes?

DR. RUSSELL: Yes. An expert.

DR. STALLINGS: A risk assessment.

DR. RUSSELL: Yes.

DR. GARZA: All right. Any others?

DR. J. ANDERSON: In the process of doing that, though, I think that we need to consider whether the onus is on the manufacturer to demonstrate that there are no problems or on the reviewers to demonstrate that there are problems, because the weight favoring additional studies is clearly different.

DR. GARZA: So you're saying where the burden of proof lies.

DR. J. ANDERSON: Yes. Exactly.

DR. GARZA: But given liability, I think, from what Roger told us, the onus is with, at least the legal onus is with the manufacturer, is that correct? I think that's the answer.

DR. HOTCHKISS: Again, to go back to the issue, those are the kinds of things that are actually done currently with things for big people

to eat. It's quite surprising to me that they are not for the much more vulnerable little people.

In other words, there are certain criteria that if you fall within this criteria and you have a group of experts who agree that you fall within this criteria, you can submit that to FDA and FDA can decide whether they like or dislike your experts and whether they agree with your experts that you fall within that criteria.

If you do, then you get what you're looking for. If you don't, then they throw it back at you and say we didn't like A, B, and C, and I would be very surprised, given the expertise in this room, that you couldn't come up with a set of criteria that said, listen, if you meet these criteria, then perhaps you could ask the agency not to conduct that term experiment.

On the other hand, if your information does not meet these criteria, then you clearly have to go to a term trial.

DR. GIACOIA: I think there are absolute and relative situations here. There is absolutely

no doubt that the very tiny premie will never be a full term, will never reach term. That is absolute, neurologically and any other criteria you can measure.

The other thing is we all agree that the outcome measure is going to be proven to be archaic in the future, whenever you have better ways to measure body composition.

The other thing is that sometimes the excuse of not having data has been equated that there is no problem, and I think that needs to be taken into account.

DR. GARZA: All right. So there seems to be, again, an evolving consensus that says term to pre-term, no; pre-term to term, a conditional maybe/dependency or depends, and that that be organized in some sort of decision tree that, in fact, would provide either a matrix or some way of providing either a method for a green or a red light in terms of a need of either term studies, when, in fact, the data are based on pre-term.

Now, let's leave it there for right now

and if I can ask the group to think during your dinners tonight, so that by tomorrow morning we can come back, say, well, what would you put into a matrix or a decision tree, not because we've got to come up with a definitive matrix or decision tree.

I don't think we either have the time and all the data before us to be able to do that in any credible fashion within the next 12 hours or 24 hours, but what we can do is at least provide some guidance for the sorts of things that should be looked at and considered that could serve as a reasonable guideline for staff, and they may want to come back to the ad hoc group and say can you flesh this out further or that's sufficient for them then to take that on advisement.

So is that a reasonable place to leave this question number one or would you like to pursue this further, before we go to number two?

DR. DWYER: I think one additional thing that would help me is it seems to me there are core measures in terms of perhaps weight, weight gain, head circumference, things like that, and then

there probably are some other things that depend on the hypothesis for why the study is being done.

In other words, if you're putting in something to change the floor, you'd want to make sure that it did that. So it seems there are core measures that you'd want to test on everybody and then there are specific probably functional indices that you would like to test on hypothesis driven reasons.

DR. GARZA: I think that is what -- at least how I interpreted Dr. Russell's comment, that one needs to look at the design of the study, the content of the study, and try to generalize that as much as possible to get precisely where you are, that there are some core things, that if there are some studies without those core values, there is no way you're going to be able to go from one population to another.

On the other hand, if those core values are there and you begin addressing specific hypotheses and the data are reasonable or unreasonable because of the nature of the health of

the population or other issues, trying to generalize those in a way that, in fact, we can discuss tomorrow and perhaps put some flesh on that recommendation.

DR. STALLINGS: The only expansion I would get us to think about is there are some other important infant formulas, for example, the pre-digestive one, that are not issues of pre-term versus post-term.

So that in the question, there was also the -- the illness. So we probably want to put those in the maybe decision tree group, as well, because if there were major changes in those, it's use in an illness setting and I think they would go in that pile. So it's not just a gestational age.

DR. GARZA: That's right. That was an example of one population to another, and it's either the pre-term to term or healthy to diseased or diseased to healthy.

DR. DWYER: Diseased to healthy, it may not be appropriate.

DR. STALLINGS: That would need to be

reviewed, as well.

DR. GARZA: That would be another one.

DR. STALLINGS: In fact, it would have to be, you would think. Good. So those come under the decision tree format.

DR. GARZA: Exactly. All right. Then let's move on then to question two. I'd ask the group to just read it quickly. I'll ask the clinicians in the group not to put Laura on the spot. They may be more reliable for this. Would any of the clinicians want to address the issue of differences in adverse events? Then we'll open it up to the rest of us that don't care for patients on a daily basis.

DR. STALLINGS: Just the issue of adverse events. Again, it really is very disease category based and that in healthy term babies, the adverse events or the events, adverse events, not necessarily attributable to the study going on, would be very different.

I really have sort of not thought about it in that way. When I had started reading this, I

thought of adverse vents being treated the way that they would be in a drug study and that there would be an immediate reportable process and all of that.

Again, it's not true because the regulatory environment is quite different and the studies are being done and the adverse events, I assume, just come into the companies.

So maybe it would be helpful to describe a little bit about the reporting structure now and give some examples to help us.

DR. CLEMENS: I'd be glad to. Based on my experience, let me share just a few points with you, Ginny. You raise good points there.

An adverse event, first of all, study designs include the possibility of adverse events based on theory, based on experience, based on everything, all publicly, if not private information that's available to get to that point of clinical evaluation.

In every IRB in which I have participated, there is a process established to report and to manage any potential adverse events or observation

that may suggest an adverse event. Each one of those is reported and then the IRB decides if it warrants further action.

That's been the case in every single clinical study that I've done, and then the IRB has the call to say whether the study continues or the subject is dropped or the study is terminated at that point.

DR. GARZA: There is no requirement to set up a safety monitor, as we heard Susan Carlson now does. That is a prerogative of the individual conducting the study and the IRB at that particular institution.

DR. CLEMENS: It's up to the IRB at that institution. Historically, every one of the manufacturers, to my knowledge, actually has a safety monitor of some kind that actually interacts with the university where it's being conducted.

DR. GARZA: Internal or is this person external to the company or the institution?

DR. CLEMENS: Typically, it's internal. Sometimes they go to a CRO and they manage the

safety monitoring.

DR. GIACOIA: Adverse events, somebody made the point this morning that you cannot estimate on a regular trial the incidence of those events, and, therefore, it will be not appropriate to base safety on the basis of those.

In other words, if the event is rare, it's going to take a much larger population, one that you could never achieve with a trial.

DR. HEUBI: I agree with Roger, but I do have to comment about DSMBs and the whole gamisch that we're confronted with right now.

DR. GARZA: Some of them may not be familiar with DSMBs.

DR. HEUBI: Data safety monitoring board, data safety monitoring plan. If you have a clinical trial now and it's funded by the NIH, you have to have a data safety monitoring board. I know this is the FDA.

But realistically, the way this is organized with most drug companies now, and I sit on our IRB and I've sat on our IRB for more than

ten years, and I have a pin here to prove it, and the issue really is it's now coming to the fore that many industry sponsors don't have an independently formulated DSMB and as a consequence, that is something that needs to be sort of pushed forward, particularly for vulnerable populations like infants, term and pre-term infants specifically.

But the issue is actually broader than that. It's that what adverse events need to be reported to them. That monitor has to be independent of the company because of potential conflict of interest and there has to be a decision about each adverse event, whether it really is related or unrelated to the formula, if it's a formula study.

And it also is dependent upon how quickly you report it, depending upon the severity of the adverse event. Most of us have mechanisms that we obviously report to the IRB, but we also have to report to, if it's an industry sponsored study, to the industry, and if they are involved, they are

committed to report to the FDA.

DR. STALLINGS: If it's a drug.

DR. HEUBI: If it's a drug. I personally don't see a lot of difference between a formula and a drug in terms of how we handle these things, because I think safety issues, particularly in vulnerable populations, we have to protect vulnerable subjects.

So as a consequence, we ought to be actually pushing forward with the same rigor that's being applied to these kind of studies that are being applied to drug studies.

That's just -- I got my soapbox, I'm sorry, but that is one of the issues that is very important. The GCRC programs in the country are pushing this forward. All the centers in the country have research subject advocate coordinators and advocates who are helping with this process to make sure that we're actually monitoring safety for subjects and studies, and most of these studies fall outside of that realm, because they are industry sponsored studies.

They are not being studied directly in the GCRC, but there is no reason why there shouldn't be similar application made.

DR. GARZA: Jim, before we go to Dr. Stallings, if you look at question two, how would you answer that differently if, in fact, there was an independent data monitoring safety officer or committee versus one that did not?

How would that impact on how you would answer that question?

DR. HEUBI: Unfortunately, I would like not to answer this question, but the real issue is that I don't think you can develop studies in terms of their sample size based upon adverse events.

They have to be on other measurable outcomes. The only thing that impacts in terms of the data safety monitoring board or some kind of plan or an officer who reviews is that that is up front that that is an anticipated part of the review and that there will be interaction with the FDA and the IRB in an appropriate fashion.

DR. GARZA: For the moment, let me try to