UNITED STATES DEPARTMENT OF AGRICULTURE

FOOD AND DRUG ADMINISTRATION

FOOD ADVISORY COMMITTEE

MEETING ON INFANT FORMULAS

Tuesday, November 19, 2002

8:15 a.m.

U.S. Department of Agriculture
Animal and Plant Health Inspection Service Building
4700 River Road
Riverdale, Maryland

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C O N T E N T S

P R O C E E D I N G S

DR. GARZA: I want to thank the committee for assembling on time. We have a very full schedule this morning, and we're going to try and conclude by 2:45 instead of 3:00 o'clock because of some plane schedules.

I think we can do this if we all are particularly careful in terms of addressing relevant points, if the points have been made, not necessarily repeating them, unless there are aspects of it that are novel to the argument, and we may have to reduce break times and possibly bring your lunch to the table in order to be able to conclude by 2:45, but I hope that that latter possibility is proven not to be needed.

I think there are no adjustments, other than those, to the agenda. Let me check to see if there are other things that anyone else would like to raise regarding this morning's or this afternoon's agenda, so we can plan accordingly.

[No response.]

DR. GARZA: No? If not, then, let's move forward.

I hope that our three presenters for public comment are here, because we're going to be starting a bit earlier.

I have Dr. Jose Saavedra, Russell Merritt, and Jon Vanderhoof. Are they here? I know Russ is, because

I saw him. Vanderhoof is here. And Dr. Saavedra--he's going to the podium. Very good. Okay.

Again, we'll have 10 minutes for the presentation, and the timer will warn you when your time is coming to an end. They'll be gaveled quite strenuously, so I don't want anybody to feel picked on if I interrupt you after 10 minutes, and then we'll go on to questions from the committee after that--after the 10 minutes are up.

Dr. Saavedra is the medical and scientific director with the nutrition division of Nestle USA, and the comments are addressing when is a clinical growth study needed.

Dr. Saavedra?

DR. SAAVEDRA: Thank you very much.

Thank you very much for allowing us to be here.

I want to thank Dr. Chris Taylor and Dr. Sue Walker for the opportunity from the point of view of the agency, and certainly Dr. Garza and the advisory committee or this ad hoc committee, for the opportunity to be able to address you this morning.

We're going to try to make our comments as limited as possible, but I do think that it is important that we are able to bring to you a few of the points that we think are relevant, particularly from the point of view of the industry.

I'm Jose Pepe Saavedra. I'm associate professor of pediatric gastroenterology and nutrition at Johns Hopkins University School of Medicine and School of Public Health, and I'm here representing Nestle.

However, collectively, with Dr. Jon Vanderhoof and Dr. Russell Merritt, we hope to bring to you a collective expression of the current status from the point of view of when these issues that you've been grappling with over the last few days and, actually, a few months, are important and how we address them as an industry collectively here in the United States, speaking on behalf of the manufacturers of infant formula in North America.

So, we don't have much time.

I want to go through a particular set of ideas that--as I said--together with the following speakers will try to give you a glimpse of the kind of effort that goes into the development of a thinking process and to the determination of clinical trials and how we go about that on a regular basis.

And the industry has currently a analysis and a process that is in place, that is used, that has been used for years, in collaboration with the agency when it comes to documentation and assessment for the use of clinical trials in pediatrics and in nutrition, particularly when it comes to infant formula.

The industry has a process and, as I said, a history through which it considers a change to infant formula for a particular benefit.

Now, we're not going to discuss claims, as it was mentioned yesterday. We're not talking safety. We can address that separately. Actually, that would probably be a whole different conference.

But we do have a process of assessment and documentation of all the important nutritional--potential nutritional impacts that any change in infant formula will bring about. This process exists and this process has been ongoing, and it keeps renewing itself.

Throughout the process and at the end of the process, each one of the infant formula manufacturers notifies the agency of all major and minor changes and all the rationale behind those changes and justifications for them.

Why is that important?

Among other things because we want to determine--based on the potential impact on nutritional adequacy of that change, we need to determine the need for clinical trials to confirm if an infant formula has and supports--has the characteristics that support normal growth--i.e., is nutritionally adequate.

Now, it is important to engage in a process that leads ultimately to that change, because these clinical

trials to be done to demonstrate nutritional adequacy, of course, need and should be done every time we can reasonably predict that there is a potential nutritional impact for that particular change.

On the other hand, I think it behooves us, as people interested in children's health and people interested in adequate running of trials and ethics, that we do not do trials that are not necessary, that are not redundant, and that we don't engage in the use of trials as a way around whatever potential change or potential impact from the industry point of view we need to have.

Now, this decision, ultimately, for the use of clinical trials in demonstrating nutritional adequacy is based on a very specific reasonable and conservative assessment of the potential impact of this change on nutritional adequacy, and again, throughout this process that becomes transparent between the company and the agency, we are always subject to review by the FDA.

Now, the industry holds itself accountable in a number of ways, and certainly, one of them is by a regular and clear process of notification to the FDA.

This is traditionally done through two types of--through separate types of changes which we divide into major and minor changes. We don't have time to go into this, and it is not the subject of discussion, but these changes, whichever, minor or major, all go through

essentially the same process of evaluation and clear understanding of the impact of that change, with notification to the agency.

Only if none of these changes apply then is it that the manufacturer continues--or makes modifications.

In essence, pretty much every aspect of the modification in infant formula, as we know it today, truly undergoes a very complex set of assessments.

Now, you have this in your hand-out. You may have had a chance to go over it last night. If not, you have 10 seconds here to memorize it.

But what basically happens is--and what this represents here is the collective--the collective decision tree or decision process that current manufacturers in the U.S. go through in understanding what potential changes, whether minor or major--and we will focus a little bit more on these--relating to packaging, processing, formulation change, or the addition of new ingredients is taken for ultimate decision on how this implementation of the change is going to happen, what information needs to be done, what documentation needs to be present before we do that.

What is a major change?

There's a number of ways to address it, but a brief definition is that it's any change where a whole new infant formula is introduced in the United States by

a manufacturer that has never produced formula or a change in current formula where experience and theory, particularly that experience and theory of the manufacturer, predicts a possible impact on nutritional adequacy of the product, or a change where there is a fundamental change in processing or composition that also could potentially impact nutritional adequacy.

Now, that change will lead all infant manufacturers to communicate on a regular basis with the agency to document very convincingly to the industry itself, as well as to the outside, documentation that demonstrates that this formula will support normal growth.

The nature of the change and the scientific rationale is what determines how much work needs to go into this process before the change is implemented and how much and what kind of supportive data are given.

Supportive data is always necessary. There is no change that is implemented without a clear process of assessment and understanding of what the potential impact of that change might be, and of course, that supportive evidence will and sometimes does include clinical trial.

Now, there is a whole process or exercise which is gone through for each one of these changes or implementations.

First, of course, we do go through what the published guidelines is, and I just do want to echo a couple of speakers yesterday who indicated that these guidelines, particularly, and a number of regulations need updated.

The industry actually does not necessarily wait for this updating. The industry tries to maintain, as much as possible, the scientific cutting edge from the point of view of what we understand are, for example, nutrient requirements in infants.

We don't wait, necessarily, for the final guidelines of somebody to show that we need to do one or other.

It was very clear yesterday, for example, that some of these regulations regarding nutrient requirements in infants need revision. They're grossly updated.

But the industry doesn't wait for that and, with notification to the agency, moves along with these changes.

We also have obviously looked at the literature, and pretty much every possible discipline that could in some way modify the change--or, I'm sorry, modify the conclusions with regards to that particular change is reviewed.

We go through all the medical literature, the nutritional literature. We certainly bring into bearing

all the disciplines, whether it's chemistry, biochemistry, physical chemistry, microbiology, to determine if this particular change might, in some or other way, modify what we need to do.

Another critical factor in this assessment is the experience of the industry, and sometimes the experience of that particular manufacturer.

The manufacturer understands--and most of them do, certainly here in the United States--understand very deeply their product. They know what goes into it. They know how the processing happens.

There is extensive documentation on all the physical, chemical changes, adulteration changes that go on in a product that they already have and that they have followed historically for years.

There is a historical component of experience that sometimes only a particular manufacturer will have on a particular set of nutrients or a particular matrix or macro-nutrient.

Certainly every manufacturer carefully measures and knows about its ingredients, its batching and packaging processes, knows its nutrient stability throughout history.

All this needs to come into bear for understanding the potential impact of that particular change that needs to be implemented, and of course, each

manufacturer also has a history of in vivo and in vitro testing in its formula, in each type, in each component, its matrix, and of course, they have clinical experience.

They have clinical experience on clinical trials, for example, that ultimately will help the manufacturer and ultimately those that are participants in the process, in the thinking process, to determine if the clinical trials that were done following or prior to this change still would support this potential change without the need for other assessments.

DR. GARZA: Thirty seconds.

DR. SAAVEDRA: Now, once we go through that large exercise, we also then, of course, engage in a very--sometimes very deep--just like you were discussing yesterday--very deep discussions as to is this going to make a difference or not, and even after that, when we're not totally sure, then we bring people like you to discuss with the industry how do we go about this change, what do we need to do, how do things need to move along, are we doing the right thing, is there caveats we have not thought about, and again, we communicate these back to the agency.

Certainly, if, after looking at this whole process --

DR. GARZA: I'm sorry, your time is up. Can you conclude?

DR. SAAVEDRA: Yes.

DR. GARZA: I'm sorry. You have 10 minutes, and if I give you more time, I have to give everybody else more time. We have 10 minutes per speaker.

DR. SAAVEDRA: With all respect, what we had requested is a 30-minute collective presentation.

DR. GARZA: All right. You can continue.

DR. SAAVEDRA: If, after all this, we are still not convinced, then we do go on to the development of clinical trials, and of course, clinical trials are necessary.

When we talk about minor submissions over the last 10 years, there's been approximately 100 minor changes submitted to the agency, approximately 360 major changes, and 50 growth studies in more than 600 children.

Collectively, the U.S. infant industry has more clinical studies and growth studies than any single institution or any single entity that we can identify.

Now, what this has done, as mentioned before and in some of your papers--this has produced infant formula that now essentially cannot distinguish, in this room, who got infant formula and who got breast milk. We've made tremendous strides.

Nevertheless, there is still a lot that needs to be done, and since that, here in the United States, with this process in place and with this implementation, not a

single nutrition-based problem has resulted from formulation changes intended and implemented by the industry here in the United States.

This is the decision tree you will have. We know we will never be able to reproduce breast milk. We'll never be able to reproduce the act of breast-feeding.

The whole point of this process--and this is what you went through yesterday--as an exercise, I believe, is try to go through each one of these changes so that these changes will apply and allow you to make decisions which, again, I think need to be made in the context of all this documentation that I mentioned earlier, which makes it very difficult to make a decision for everything or make a recommendation that is a blanket statement.

I will now ask Dr. John Vanderhoof to continue our presentation. This particular aspect will relate to the comparisons and groups that need to be incorporated into the measure of clinical trial.

Jon?

DR. VANDERHOOF: Thank you very much.

Until eight weeks ago, I was an academic myself, and now I have this new job, and I'm looking at this from a new perspective, and it turns out, I guess, it's

probably not all that different than how I looked at things before.

What I want to do is just tell you very briefly a little bit about the "what" part of the study process, and then Russ Merritt from Ross will tell you a little bit more specifically about exactly how we conduct clinical studies.

The first point I want to make is that what we've been doing for the past several years, since 1988, is based upon the AAP committee nutrition guidelines, and I think these have really served us very well.

We've had a longstanding history of producing nutritionally adequate formulas, and whenever we do clinical studies, safety is, of course, a given.

This is something that's well worked out during the pre-clinical phases. Those questions have, by and large, been answered, and at this point in time, we're ready to demonstrate nutritional adequacy with our formulas.

As everybody mentioned yesterday, the timing of doing a formula study is very critical. You need to do it during the first four months of life, when infant formula is the sole source of nutrition for the baby and the baby is most vulnerable and its most rapid growth phase, so that we do want to study the formula at the

time when its performance could most likely be critically evaluated.

Weight is the predominant end point that we want to measure. It's the most sensitive indicator of nutritional adequacy, and it's our primary outcome variable.

Secondarily, we measure length. One thing I learned from taking care of lots of children with chronic liver disease is that weight gain is not always a good thing, and so, we have to measure length, as well, and I've added head circumference. While we don't feel it's mandatory, it's a nice cross-check to have available to us on length, and we can address gender differences by co-variant analysis.

There may be some instances when we might choose to look at specific laboratory measurements or other body mass indices or something, and those are the times when we might want to have a specific nutrient change or a specific nutrient that we put into the formula that might affect one specific biochemical parameter, and at that point in time, we would expect to introduce additional laboratory measurements.

We usually do double-blind, randomized prospective studies in most instances. This has been for many years the gold standard for clinical research.

You might say, well, why would you want to do this if growth data are inherently objective measures and you know how babies are supposed to grow.

I think there are a lot of times when we do clinical studies that we're also interested in looking at some secondary parameters and we want to find out if there are differences between the new formula and the old formula, and we might also be interested in finding out if the incidence of adverse events that might be picked up in the study are the same between an old formula and a new formula, and at that point in time, we would definitely want to have a control group.

Our studies are powered to detect a mean difference of 3 grams per day, and a weight gain is a primary outcome variable. This is based on the AAP guidelines, and since this standard was adopted, there have been no product withdrawals because of nutritional inadequacy, and we think that these guidelines have served us very well in the past.

Presently we're facing a bit of a problem in that there are a limited number of subjects available because of the increased breast-feeding rate and a decreasing birth rate, and we have looked into the possibility of powering studies to detect smaller differences.

And if you do the math on this, for example, if you did a study that required 500 infants, by the time you looked at the incidence of breast-feeding, the patients that weren't acceptable, and then the number that--the 10 percent that would actually volunteer and then the drop-out rate, you would have to screen 24,000 infants to come up with that 500, and at the present birth rate, that's about the population that you'd see in new births in a city of 2 million people.

So, what other options are there?

Well, there are basically historical controls and reference data. We have a large volume of that kind of data available.

The advantage of using reference data is it minimized drift over time and identifies it. For example, if you look at formula A and compare it to B and then the next study you do is compare B to C and then C to D, each one of these formulas are a little bit different, so they may statistically come out the same.

But if you compared A to D, you might miss something, and you can pick that up when you use historical data, and if you didn't have to have the control group, then you might be able to power the study at a little bit higher level.

Ideally, most of the time when we conduct research, this is what we would want to do. We would

want to use concurrent controls so that we could identify these other things that we talked about, like the incidence of adverse events and so forth.

We would want to compare the mean data that we have to the mean reference data to make certain that we don't have any drift, and the vast majority of times, or at least frequently, this is the kind of study that we want to do.

So, in summary, we think that the present criteria that we've utilized since 1988 provide an ideal balance of allowing very nice research to be done on infant formulas and, at the same time, protecting too many infants from undergoing formula studies and subjecting an excessive percentage of the population to studies.

We think that the present guidelines have resulted in superior infant formulas and an excellent record of ensuring nutritional adequacy for our population.

Powering the studies according to the AAP guidelines has produced an excellent safety record, and we're very happy with the results that we've had using these guidelines.

Regarding the specific questions that you may be pondering at the moment, it's our opinion that concurrent controls in formula studies are usually desirable but in

some instances may be unnecessary, and it may be appropriate to use reference data in some form.

We also feel that most of the time the weight and length measurements and head circumference measurements that we talked about are the primary variables that we want to address, but occasionally other biochemical or body mass measurements might be indicated in specific circumstances where the particular study might indicate their value.

I'd like to now introduce Russ Merritt from Ross Labs, and Russ will tell us a bit about exactly how we conduct growth studies.

DR. GARZA: Thank you, Dr. Vanderhoof.

DR. MERRITT: Thank you for the opportunity to address the committee this morning. I'm going to pick up where Dr. Vanderhoof left off and talk a little bit more about the "how" of conducting studies.

The infant formula industry has provided you a sample growth protocol for infant growth studies that reflects our experience with conducting such studies since before the inception of the Infant Formula Act in 1980. I hope you've had an opportunity to review it.

There are a number of specific aspects of this study design that I'd like to call your attention to.

The first is to recognize the purpose of a regulatory growth study.

We need to remember that infant formula is food, food for a vulnerable population and, at times, the sole food, but still food.

This food supplies the nutrients required for infant growth within a range considered acceptable.

We need to specify testing of new infant formulas that provides assurance that they support growth during the fastest period of human growth, when it is used as the sole food in the diet--that is, in the first four months of life. After four months of age, the common use of other foods in the diet make it much more difficult to assess the data in a growth study.

The method of achieving this is to demonstrate that a proposed new infant formula performs at least as well as a current commercial formula appropriate for the population under study. In some special situations, additional claims may be sought and additional studies or end points will be needed.

Now, as far as control groups are concerned, accepted clinical practices generally require the comparison of a new intervention with a standard current of practice--in this case, a marketed infant formula.

To put the growth study in an historical context, the growth data are always going to be compared to some reference standard such as the CDC 2000, the Iowa

data, or internal historical data, which may be more extensive than some of the reference databases.

So, in effect, a current control and an historical reference play different roles in the growth assessment.

The use of an exclusively breast-fed reference group, historical or concurrent, assumes that the group of formula-fed infants should grow identically to this group.

As of today, no well-recognized standard for exclusively breast-fed infants exists, thus the WHO study we heard about yesterday that is underway.

We cannot assert at this stage that we know that the growth of a breast-fed and formula-fed infant should be identical or that a specific feeding regimen has unequivocally been demonstrated to be better than others from the perspective of long-term growth and body composition.

Furthermore, different initial growth patterns may turn out to be preferable from the standpoint of different clinical outcomes--for example, neuro-development, obesity, cardiovascular risk, etcetera.

We move to one-sided versus two-sided.

One-sided testing addresses the critical question of whether the new formula performs at least as well as a current commercial formula.

That's the question we need to address, and in contrast, two-sided testing, as usually performed, is less sensitive because it dilutes the power.

If we look at the sensitivity to measure nutritional adequacy, it's not certain that very small differences between groups are necessarily meaningful.

The existing de facto standard of 3 grams per day, approximately a half a standard deviation, appears to have served us well. At this stage of our knowledge, we simply do not know the best infant growth pattern, especially not for the individual infant in a study.

For context, please bear in mind that studies to define longitudinal growth status that are underway--for example, the WHO multi-center study--are actually smaller than the studies that some food advisory committee consultants have suggested to verify that a single new infant formula, which will already be known to contain the necessary nutrients, supports growth.

So, some of the suggested protocols are actually greater, numbers of subjects are actually greater than what is being used in that study.

We've also heard repeatedly from the consultants that it's a misuse of the available science to pretend we understand the health implications of a gram or two of weight gain per day for a short period in human life or to define an extraordinarily specific statistically-

driven definition of a single rate and pattern of infant growth as the only one that is normal or even acceptable when testing infant formula.

What we're trying to get to is an actionable protocol. The growth protocol provided by the industry acknowledges the important need to continue to provide assurance that new formulas support normal growth.

Although the outline submitted is brief, the actual protocol may extend to 80 pages or more, as specific details are filled out in a specific instance.

The Infant Formula Act places a responsibility on manufacturers to demonstrate that their formulas can function adequately as substitutes for human milk.

To date, the manufacturers have met this obligation effectively, often through the use of a growth study.

The growth protocol utilizes the current scientific approach of a randomized, blinded, control trial in conjunction with well-characterized reference data for infant growth.

A couple of comments on the evolving context in which we do these studies.

This is not a static environment. The nation is coming closer to the Health People 2010 goals for breast-feeding. This will have the effect of reducing the

number of exclusively formula-fed infants available to participate in clinical trials.

In addition, evolving ethical standards may further limit the types of studies acceptable in pediatric subjects.

Such changes may make it increasingly difficult to complete even the growth study protocol which industry has used.

Thus, rather than moving to more restrictive protocols, other approaches regarding study participation, eligibility, and/or fewer subjects for the use of historic references may need to be considered in the future.

The current system has effectively protected the public health while allowing more than 20 new infant formulas to enter the marketplace in the last 10 years.

We welcome a more predictable process and regulatory environment, as well as the collective expertise which the Food Advisory Committee and the FDA have brought to bear here today.

However, in your deliberations on these issues, we do ask that you be mindful that more restrictive standards may not achieve any greater assurance of nutritional adequacy but could substantially reduce the ability of industry to bring the benefits of new science to infant nutrition in a timely fashion.

Thank you for the time.

DR. GARZA: Thank you, Dr. Merritt.

We have a choice--we have one more speaker that has come forward--to hear the additional speaker and then ask questions to all four, or you can--we can take the time now to ask questions to the first three speakers. Is there a preference among the group?

Do all four? That would be my sense, as well.

I'd like to then call Ms. Barbara Heiser--I hope I'm pronouncing that name correctly--executive director of the National Alliance for Breast-feeding Advocacy.

Ms. Heiser, I'll warn you about 30 seconds before your 10 minutes are up.

MS. HEISER: Thank you for taking the time this morning to let me speak before the committee. My name is Barbara Heiser. I am the executive director of the National Alliance for Breast-feeding Advocacy.

I'm a registered nurse and also an international board-certified lactation consultant.

I guess, to start with, yesterday, as I sat and listened from the back row, I wanted to stand up as we talked about optimal infant feeding and say wait a minute, we're mammals, our milk is species-specific, human milk for human babies. That's optimal feeding.

That doesn't mean that the other formulas and all aren't important and shouldn't be good. They should.

But we know optimal feeding is exclusive breast-feeding for six months, not even four to six months, six months. That's been decided after at least--I've been in discussions internationally for 12 years on that subject.

It has been reviewed, literature, research, everything, and optimal feeding as exclusive breast-feeding for six months has now been agreed upon by the American Academy of Pediatrics, by the Surgeon General of the United States, as well as WHO.

So, I think that has to be our standard. Does it mean that formula feeding has to have the same growth pattern? I don't know. But when we say there has to be a standard, we should have the standard that we know is best for babies.

The other thing that NABA has worked on very hard is speaking for breast-feeding moms and babies.

We don't speak for any group or professional organization; we speak specifically for breast-feeding.

As a mother, I don't think the government agencies understand how much trust the general public put in you.

When a formula--when something new comes out, they've heard all the reports about how drugs take years and years and years to go through testing before they go to the public and they think that's true of everything.

Recently, with the addition of the long-chain fatty acids--DHA and ARA--moms think it's wonderful.

However, the marketing has been so wonderful that mothers are afraid--well, they're happy. They call me up and say which formula has the breast milk in it.

And then yesterday I got called--and you'll appreciate this if anyone's from California. It was from California, and a mother went to the WIC program, because they're working on contracts right now, for the new formulas, and she says whose breast milk is in the formula? I want to know, because I want to know if it's safe. Okay.

That's how it's been perceived, and we know that the DHA and the ARA that's been added is fermented micro-algae and soil fungus, whatever it has taken to produce this--these aren't even in our normal food chain, and we're having a lot of babies have problems with this.

Now, yesterday, one thing that had not come to my attention previously was the liability factor as far as hospitals, food poisoning, adverse events.

Most of the people working at ground zero with moms and babies don't know lots of babies have allergic reactions or problems with different formulas.

That's why there's so many out there for them to try and why each company makes different kinds.

But we're seeing a lot more explosive diarrhea with this, and we've been wondering why some of the reports--in looking at post-market surveillance, just in my mind as a mother and an advocate for women, I worry that the 4 million babies being born in the United States are being guinea pigs for post-market surveillance without the mothers knowing that it's being looked into if formulas are safe.

They think it's already been through 10 or 12 years of testing, and I know the companies do a lot of testing, and I appreciate that, and I want to say that I believe infant formula is a very necessary part of our society. I was a NICU nurse. It's very important. But I want to make sure it's the very best product and it's perfectly safe for our babies.

Also, as a mother, we talk about easy growth measurements--height, weight, head circumference--very easy to get, very now, but that wouldn't be what I want to know about this food to my baby.

I want to know that it's giving everything, and we know that the important thing for growth for human babies is brain and neuro-development, and so, I really ask the committee to look at the regular growth parameters. They're very important.

But you have to have some looks at the neuro-development, also. It's been hard to find because of the marketing.

I mean I hear the companies now say that there's less totally artificially-fed babies out there, formula-fed babies out there, and that's funny, because we've had the same thing on the breast-feeding side.

Because of marketing and supplementation, there's been fewer and fewer exclusively breast-fed babies out there.

But we need to look at it, and I was excited yesterday, hearing about what you're doing, because I thought, you know, okay, we know optimal breast-feeding is exclusive breast-feeding for six months.

Now, as FDA is doing some studies on new formulas and ensuring, the topic was brought up, you know, well, how do we know if a new formula starts the growth pattern of a breast-fed baby that it's really still meeting the nutritional needs? Well, if you're doing your study right, we'll know, and we'll have the proof that the formulas are just as good as they can be, and I think that would be very important.

The last thing I want to say is, once again, mothers expect safety from the government more than you know.

They expect great products from the companies. You have a great burden. When a health-care provider gives a mom that discharge bag full of the goodies, it's like the health professionals are endorsing that product to them.

And so, what I ask of you on this committee is, as you deliberate and set up growth standards, please know that breast-feeding is optimal for six months, and please find out what's best for babies on infant formula and what's the safest for them.

Thanks so much.

DR. GARZA: Thank you, Ms. Heiser. Before you leave the podium, don't take your microphone off. There may be some questions, and we'll take questions.

Does the committee have any questions of Ms. Heiser?

Dr. Stallings?

DR. STALLINGS: Thank for being with us.

As a point of clarification, I'm not sure that the American Academy of Pediatrics Committee on Nutrition has endorsed six months of exclusive breast-feeding.

MS. HEISER: In their latest statement, they have.

DR. BAKER: I'm a member of the Committee on Nutrition, and we have not. The official policy of the Academy of Pediatrics is still four to six months.

There is a new yellow book coming out which will have new recommendations, and it's not decided yet what that will say.

MS. HEISER: I'm sorry. I gave that information from the United States Breast-feeding Committee on which AAP does sit, and Dr. Larry Gartner gave it to us. So, if I mis-quoted, I am sorry, but I had it from a primary source.

DR. GARZA: Are there other questions?

Ms. Heiser, you mentioned that there's an increased rate of diarrhea and other illnesses or intolerance.

Is that from monitoring information that your organization collects, or is that based on your professional perception, or can you give us a bit more information on that?

MS. HEISER: The information I can give, unfortunately, is only anecdotal, but as a organization, we do collect information. We encourage mothers to report adverse events via Med-Watch and to report to the companies, as we do when we train nurses, etcetera, and we've been doing this for the past several months, because initially, when I heard of it, I just thought it was one incident, and then I heard it again, and we lecture throughout the country, so we have had a pretty good report.

The most recent one came from the State of California, the WIC program.

A lot of the mothers there were buying formula on their own because they wanted the best for their babies, and they reported large number of cases of explosive diarrhea, to the point that the WIC director, when they were looking at the contracts for the upcoming year, was concerned if that was the only product they were going to have available to their population.

DR. GARZA: Any other questions?

Dr. Downer?

DR. DOWNER: Thank you for putting a human face to this.

I wanted to find out, with respect to the anecdotal evidence that you've been collecting, have you looked at all at how the formula is being handled with respect to safety issues, to see if this may be impacting on, for example, the explosive diarrhea that you mentioned today?

MS. HEISER: Yes, we do question that. We've been asking specifically health professionals with babies in NICUs and in the hospital setting where we have total control to really look at that issue, so we'll have some information. As of yet, that hasn't been gathered.

But from the general population, we're getting more cases of it, and these are the same people mixing and doing other formulas, too, without it.

So, I see them as their own control group, because they're using both kinds.

DR. GARZA: Dr. Stallings?

DR. STALLINGS: I was interested in your comment that the public perceives infant formulas as, in essence, being managed more like drugs than like food.

Could you make a few more comments on that and the basis--the information that led you to make that summary statement?

MS. HEISER: Okay. The reason is, initially, with health-care providers, because a lot of the information goes into food and drug through Med-Watch and also because of the promotion by the companies to hospital personnel, they are treated as vendors on the--you know, as drug vendors more than the PO office for the foods down in the cafeteria, okay? So, that's the beginning of it.

The other is, as claims come out, health claims and all, as that comes out, then people look at formula as more than just a bowl of cereal, okay?

They know it's important because the Academy of Pediatrics has said don't give regular milk for one year.

You know that the baby needs more in its growing time, that it's very important that it has this thing.

We still have grandmas around that remember pediatricians making up their own special concoctions of formula to meet those nutritional needs.

So, this is where that perception comes from, that it's not just something you can go out and get.

DR. GARZA: Thank you very much, Ms. Heiser. We certainly appreciate your taking time with the committee this morning.

And I'd like to ask Doctors Saavedra, Merritt, and Vanderhoof if they would please come up, and I think it will be easier for us to ask questions if the three of you are up at the podium, assuming that we will have some.

Dr. Stallings?

DR. STALLINGS: Thank you gentlemen for being with us.

I'm interested in having you discuss the issue, really, as the one-tailed versus the two-tailed analysis, because I think all of us--and I certainly know, including all of you, are interested in the issue of over-nutrition, as well as under-nutrition, and that seems to be one of the core issues that we're dealing with.

So, could you make a few comments and, in some ways, try not to do the practical issue, because I'm asking you more of the theoretical question now.

I know it takes twice as many subjects or almost twice as many.

Thank you.

DR. MERRITT: I'll start, since I brought that up.

The historical context has been to assure nutritional adequacy, and in that context, if you look at how the study is designed, if you were to put all of your power on the lower half of the study, then, in effect, you have greater sensitivity to detecting a problem on the low side.

Relative to additional protections on the high side, as Jon and I both noted, we not only will generally compare a new formula or a modified formula to an existing formula but also then check these data against a reference standard, whether it's CDC 2000 or Fels, etcetera, and in general, what we find is concurrence of the two answers.

I think if you--if we were in a situation where there was not concurrence of those answers, we would, you know, do some additional thinking and some additional assessment.

So, I think you have the dual assurance of somewhat greater sensitivity on the low side but also the cross-check against your historical norms.

DR. GARZA: Dr. Denne?

DR. DENNE: You told us there had been 150 major changes and 50 clinical studies, and I was wondering if you could tell us--give us an example or two of a major change that didn't require a clinical study and the rationale behind that.

DR. SAAVEDRA: There's a number of examples.

For example--and there's many ways to try to understand the--I think what's critical is understanding the process, the thinking process, because that's really what you're all charged with, is understanding if that major change--for example, a particular ingredient in a new formula--is going to be impactful from the point of view of nutritional adequacy.

So, a particular ingredient can be added to a formula that has slightly changed from the point of view of the manufacturer's matrix over a period of time, and we add that ingredient, which has already been tested, which is already GRAS, which has already been analyzed biochemically in terms of nutrient stability, in terms of physical chemical stability, in terms of possibility that could adulterate other products and so on and so forth.

So, because it is a new ingredient to that particular product--for example, a soy formula versus a milk-based formula--then that is a major change.

However, extensive experience with the basics of understanding of that ingredient, as well as the formula, and all the interactions that could possibly happen, that we could identify within that--for that change don't necessarily mean that you need to study 100 or whatever number of children to demonstrate that it is safe and that the formula hasn't changed from the point of view of providing nutritional adequacy.

So, these are major changes, and they're classified that, and I don't think we're going to go into the discussion of a particular major change.

But this is an example in which a growth study would essentially be unnecessary if there has been all the evidence from the point of view of the ingredient, from the point of view of the product, and the manufacturer's understanding--I think this is critical also to understand that each manufacturer knows very well its matrices, its proteins, its fats, and every ingredient that goes in there, so that this predictability from the point of view of potential nutritional impact can be established.

DR. GARZA: Dr. Anderson?

DR. ANDERSON: I'm going to suggest two criteria for the setting in which clinical growth studies are not required and ask you to comment.

The first would be that they would be required only when there is a reasonable basis to predict that a change to a formula will materially impact nutritional adequacy or otherwise have a significant adverse impact.

The second would be that they're not required when the preponderance of the evidence suggests that a change will not affect the ability of the formula to promote normal infant growth.

The emphasis is really on--I've tried to formulate these in a way that--in the first instance, the assumption is really that the change is safe unless otherwise--unless thought otherwise, and in the second instance, one needs to demonstrate safety in order not to proceed with a study, and I wondered if you could comment.

DR. VANDERHOOF: I'll try that one.

First of all, I think if there's reasonable likelihood that--or even a reasonable suspicion that the formula might adversely affect growth, we probably would choose not to even test that.

So, we would only want to test a formula clinically that we were quite certain was nutritionally adequate.

And then to take that a step further, I think unless we were extremely certain that there would be no adverse effects on growth, we would want to do a growth study on the babies and particularly any kind of an ingredient change or anything that might somewhat affect any parameter that involves growth, such as the changes in the hormonal milieu or tropic factors or anything like that that could be secondarily affected, would certainly trigger a growth study to be done.

I think there are other instances, as Pepe mentioned, when certain ingredient changes would predict absolutely no effect on growth, and in that instance, you may not need to do it if the manufacturer has extensive experience in that regard.

DR. GARZA: Dr. Stallings?

DR. STALLINGS: You all were with us yesterday when we had the good fortune of having Dr. Fomon recap some of the history that, you know, I'm sure informed the 1980 law and then the 1988 Academy of Pediatrics advisory group which put together the things that we're currently operating under.

And at that point, he was saying that the 3 grams a day, you know, basically was an opinion at that point based on those data and a little bit of good clinical judgement, which often informs all of it, and then yesterday we had, if you will, a group getting

together and considering the same thing, and my sense of what we heard yesterday is that 3 grams a day difference may be higher than it should be and that we might be well-informed to reduce it a little bit.

So, I was interested in your comments, knowing all of you have been through the opportunity to serve on consensus committees and recommendations and that sort of thing, but I think I was hearing that that number, which may have served us well in the past, might need to be revised.

I'd be interested in your opinion on that.

DR. VANDERHOOF: I'll give you my opinion, and then maybe this is an important enough topic that we probably all ought to comment on it, but this is an arbitrary number. I think that's probably where it came from. Somebody had to pick a place to start.

Here you try to strike some kind of a balance.

You know, if you want to do a controlled study with a control group and get an appropriate number of babies and whatever and you power it to that level, I think it's reasonably practical in terms of not subjecting too many babies to clinical studies and, at the same time, getting the information that you need, and remember, this is where we power the study, and in actuality, what happens is that the curves are normally

quite similar, and that's not to say that we expect to see that kind of a difference.

I think if you go beyond that, then you have to start looking at other situations where you might need to eliminate control groups, and that then has a negative on the other side of the equation.

So, there may be instances where it might be necessary to power the study differently, but I think for the vast majority of cases, this is probably adequate, and it's certainly done well for us in the past.

Russ?

DR. MERRITT: I think if we had greater assurance as to what's best, I could have more enthusiasm for trying to get closer to that standard, but in the absence of that knowledge and the history of protecting the public health with the 3-gram standard that seems inherently reasonable, as well, I'm not convinced we've made the case that, in fact, a different standard will give you additional assurances.

It will certainly increase the time and the number of babies and such that will have to be involved in the studies in order to bring new formulas or make changes in formulas.

So, I think in the absence of that kind of certainty about the standard, it makes it very difficult to rigidly pursue it.

I've looked into, you know, the historical differences that we've seen recently, and although we've powered the studies for 3 grams, in almost all instances the actual difference is quite a bit less.

DR. SAAVEDRA: I just want to add--I certainly concur with what Russ and Jon said, but I do think that, aside from that--and certainly I'm trying to understand as best as possible what is ideal, which I know none of us can actually say what is ideal.

In the absence of that, it is striking the balance between what is practical, what is doable, and what is beneficial.

I mean I think the goal here, if we want to do something that allows us to make improvements and enhancements in infant nutrition--and we have--as we said before, we've come a long way--it's striking the balance that we as--and all of you as academicians have to grapple with all the time, and these differences of three grounds that we're talking about is between the control and the experimental group.

As we discussed, for example, in Jon's talk, there can be drift. The difference may be 3 grams for that group but may not be with the reference population or may not be between two different groups that were compared to the reference population.

So, until we know what is the right one that we're comparing to, then trying to find minute differences and smaller and smaller differences--which, of course, in the ideal situation, in the non-human situation, which is the ideal one, it would be doable--we need to do our best to strike that balance, and I do think we need to take history into consideration, and I did mis-quote, I said 600 children instead of 6,000 children, but that's the kinds of numbers that have evolved into having the kinds of formulas that we have now.

DR. GARZA: Rather than addressing the 3-gram issue, I have a more generic question. Each of you referred--I think each of you referred that you would be supplying data demonstrating the support of normal growth. What is normal growth, from your perspective?

DR. MERRITT: What I thought I took home from yesterday's comments here was that there are a lot of opinions based on our scientific experience, based on our bias, based on our personal preference, but a definition of normal beyond the context of what has historically happened is very difficult, and I think the knowledge has simply not reached that state.

So, I think we have a default definition of knowledge of normal that reflects, for example, in the first few months of life, NCHS or Fels or the historical

data that are available to us and that, much like, you know, an acceptable daily intake, this is the experience that appears to be associated with reasonable health.

DR. GARZA: Dr. Merritt, before you pass on the mike, in the absence of ideal information, which we often deal with in medicine, we often to go to defaults and often in terms of normal physiology and history.

I have not understood the rationale for saying that, in fact, one can't use, in the absence of whatever one might define as ideal information, the growth patterns of breast-fed infants as that normal standard, and notice I didn't use the term "reference" but "standard," precisely for the reasons that you've outlined, that, in fact, we don't have ideal information available to us and that we have to depend on some default and that, until proven otherwise, the breast-fed infant becomes that standard.

What is faulty with that rationale?

DR. MERRITT: I think we already know that, at some stages, probably less in the first three to four months than subsequently, there are some differences between the breast-fed and the formula-fed infant.

We've also seen that, by approximately two years of age, they appear to come a little closer together, and picking up on something I think Jon said earlier this morning, I don't think, at 10 years of age, we have the

ability to look back through the retrospectoscope and say who was breast-fed versus who was bottle-fed.

And we certainly, at this stage, do not know the implications for, you know, the chronic diseases of later life, as well as even neuro-developmental issues, as to what particular mode of feeding or combination of foods or combination of breast-feeding with or without supplementary foods is truly going to give us a particular outcome at some lengthy time point remote from the feeding experience.

DR. GARZA: But if that's true--I need to press this, because it's an issue that we're going to be dealing with once you get off the podium.

If that's the case, then we have a historical experience of millennia with human milk feeding, a rather recent experience with formula feeding.

In the absence of that type of information, why not use the breast-fed infant as the default?

I mean I am failing to understand the rationale that, because we don't have information, then, in fact, we have to rely on historical information, but if we rely on historical information, then we've got the historical information of the feeding patterns for millennia. How do we get ourselves out of that bind?

DR. VANDERHOOF: Well, let me make a comment, and then I'll turn it back to Russ.

As a clinician, we've all had experiences in dealing with children--breast-fed children with failure to thrive, and one of the first things that you do is change the mode of feeding and find out how well the baby gains weight.

And very frequently, the baby will markedly increase their formula consumption and they'll gain weight very rapidly, and when you look at the feeding patterns for breast-fed babies, I think you have to consider that there are probably a fair number of babies in that group that are probably not getting as many calories as they might want, because the process of feeding the baby is different.

And so, if you simply look at this as a nutritional component problem, I think you may be missing the differences in process, that the process of breast-feeding, the interaction between the baby and the mother, the cues for the baby determining when--and the mother determining when the baby's had enough to eat and so forth are all significantly different, and so, this factor--these factors may influence the differences in weight gain, as well as nutritional factors.

And if we go back--and then, within infant formula--I think somebody brought this up yesterday--I'm not sure who it was--if we go back and try to replicate that by changing the nutrient mix in the formula, we may

end up depriving the baby of essential nutrients that it might otherwise need.

So, I think the problem is there's an additional difference in process, as well as formula.

DR. GARZA: Without a standard, Dr. Vanderhoof, what prevents the formula industry from manipulating the composition to match any other standard or any other reference?

If one can do that to, in essence, match the breast-fed infant to create the sorts of problems you just described, doesn't that argue that, in fact, one could do it in the other direction, as well?

DR. VANDERHOOF: We could probably make a formula that could duplicate the growth curve of a baby that's breast-fed, but you'd have to do it by making a formula with the caloric density significantly lower than breast milk, and it's been our standard to try to replicate as nearly as we can what's in breast milk when we create the formula.

So, the only other way to do it would be to feed the baby less milk.

DR. GARZA: In fact, that would not meet the nutritional standards of present law if you did that, right, if you manipulated it in that fashion.

DR. VANDERHOOF: That's right.

DR. GARZA: Okay.

Are there other questions?

Dr. Heubi?

DR. HEUBI: On a totally different vein, the question that was raised, I think, by Ms. Heiser this morning was one that I think we addressed at our last meeting here, and that was the reporting of adverse events related to formulas, and the comment was made--and I don't remember who made it in April--the comment was made, I think, that many reports are made to companies that don't come to Med-Watch regarding adverse events related to formulae, and Ms. Heiser was making this comment about introduction of a new formula, and now there are myriad complaints.

Can any of you comment about this and how this work vis a vis the agency and the individual companies?

DR. MERRITT: In accordance with the Infant Formula Act, we each have mechanisms for both recording and assessing all complaints of any type relative to infant formulas that are reported to us, and the FDA examines those on an approximately annual basis to--along with us--identify any potential issues that may have emerged.

And we are highly responsive and, I think, responsible in this regard in terms of the effort that goes into the record-keeping and the assessment of those complaints, and in some instances, for example, when a

new formula is marketed, we will review those at periodic intervals to make sure there isn't something happened in the marketplace that we had not been seeing previously. So, I think those safeguards are in place.

DR. HEUBI: Let me ask one question beyond that, and that is there was--there's been discussion, at least at the NIH and other agency levels, about having independent monitoring boards, and I know that most industry has their own internal, and then there's this obvious potential for conflict of interest in terms of that particular scenario, reviewing your own data, saying, oh, there's not a problem. Can you comment about that?

DR. MERRITT: I think for a standard growth study of the type that we're describing here for changes within the realm of a change in the formulation but not a dramatic change in claims, for example, on the formula, there is enough experience and enough guidance in the form of the International Conference on Harmonization and the like relative to how these studies are conducted that I think that would be, at least in my impression, an unnecessary degree of oversight.

Now, there may be special situations when you're studying special populations and making more novel interventions when an external advisory board may, in fact, be indicated.

DR. GARZA: Dr. Briley?

DR. BRILEY: Yes. I'd like to ask a question.

I understood that you said that, when you did a product testing such as soy, that you knew all the scientific background and all of the chemical background, the physiological background, but I guess I didn't understand or maybe you didn't come across--how would you know if that product was absorbed, utilized by the child unless you had done a clinical test with that new product?

DR. SAAVEDRA: What I was talking about is, for example, the addition of a particular change in a ingredient in a soy product that has been used and has clinical trials already.

Of course, a change in the protein, a change in the protein source is what would be considered a major change, and actually, that would be a very good example of a time where you do need a growth study, if you're using a protein that has not been used before.

So, from that point of view, absolutely, this would be a very good example of one of those situations where a clinical trial is pretty much self-evident from the beginning.

DR. MERRITT: Bear in mind, that would be done in the context of what was already known, for example,

from the animal literature and the like that demonstrated the availability of the protein source.

DR. GARZA: We are going to give Dr. Kuzminski the last question, so we can stay on schedule.

MR. KUZMINSKI: One of you--I believe it was Dr. Saavedra--described the use of pre-clinicals, both in vivo and in vitro, prior to clinical testing.

Could you provide us with a little bit more detail on what these pre-clinicals are and some idea of the reliance on the use of them in contrast to going to a full-scale test?

DR. SAAVEDRA: Yes.

The in vitro studies have to do with a number of characteristics of the product that relate to chemical, bio-chemical, physical chemical studies that are actually done in the product to measure the stability of the ingredient, the fact that the ingredients that were previously there didn't change, didn't become adulterated, and so on and so forth.

So, there's extensive trial work that goes on, typically, at the--what is part of the R&D phase of a particular product to make sure that, from the structural, chemical, and physical chemical characteristics that might in some way modify a particular or interact with another particular ingredient within the formula don't happen.

If they do, then, of course, this typically requires further assessment to decide if this is even a viable product.

Many times the change is dramatic enough that there is not worth in continuing that kind of modification, because the in vitro work actually demonstrates that the change is significant enough that it might actually have more nutritional impact that you would think.

I do want to emphasize that once we go to the clinicals following those studies, it's because we have--for the most part, the industry feels very reassured that there is no nutritional inadequacy.

I can assure you--and I'm sure you all as clinicians would not test a product that you don't think is going to be the same or better. That happens only after you've gone through this, as I said, extensive exercise where you do this kind of testing to understand better these changes before you even give them to animals and then before you give them to humans.

MR. KUZMINSKI: So, the in vivo part of the pre-clinicals are animal-based.

DR. SAAVEDRA: Usually, yes.

DR. GARZA: All right. I certainly want to thank the three of you for your patience with the committee and your help in our deliberations. Thank you.

DR. SAAVEDRA: Thank you.

DR. GARZA: On the agenda are final questions to invited speakers. I don't want to--I think the word "final" is perhaps too final. I think that most of them have been willing to stay throughout the meeting and will be available to us, but having reflected on the discussions yesterday, I want to check with each of you to see if there are any questions you may have to any of the presenters before we continue with question four, where we left off yesterday.

Dr. Stallings?

DR. STALLINGS: I felt like, after yesterday, I had a much better understanding of how modern breast-fed and formula-fed infants grow compared to the different references, but I didn't think I came away with quite as clear an idea of how breast-fed and--modern breast-fed and formula-fed babies are growing compared to each other, because a lot of the demonstrations we saw were really reflecting the idiosyncrasies of the growth grids that we have today and how--going from the '77 to the new 2000 and potentially to the WHO.

So, I wondered if Ed or someone might be able to address looking at that and trying to focus on the difference in growth in the first four months or the first six months.

DR. GARZA: Ed, do you have any of those charts with you?

DR. STALLINGS: I don't know if it's helpful, but that's why we had the chart brought in.

DR. FRONGILLO: Well, let me tell you what I've done, and you can ask me how you want to display it, okay?

Virginia asked me about this first thing this morning, so I was sitting here playing with my computer, calculating these rates.

I have brought with me--happened to bring with me the Iowa data and also some data from Newfoundland that Alex Roach and team collected.

The Iowa data are expressed in terms of rates from eight to 42 days and then from 42 days to 112 days, and basically, there, in the eight-to-42-day period, there is really no difference for males or females in rate between breast-fed and formula-fed.

So, in the early period, from eight to 42 days, there was no difference, but in the period from 42 to 112 days, roughly a little past a month to almost six months, that--four months, I'm sorry--that there were differences for weight of about 3 grams per day, with the formula-fed being faster, and a difference--a really quite small difference in length, in millimeters per day. It's in

the order of .07 millimeters per day, which is--I think we can all agree is really small.

So, essentially we have differences of--for males, it was 3 grams per day and for females, it was 2 grams per day.

DR. STALLINGS: There was a gender difference in the second interval.

DR. FRONGILLO: Right. Okay. So, that was for the Iowa data.

So, basically no difference in the early period and some difference, 2 to 3 grams per day, in weight for the second period.

The data in Newfoundland--those data--I actually showed some of those data in my presentation yesterday.

There were data on breast-fed infants and then three different formulas. So, I averaged together all the data from the formulas, so we can just have two groups.

And there, it was zero to two months, two to four months, four to six months.

There there's a different pattern, because in the zero to two months, the breast-fed infants for both males and females grew about 3 grams per day faster from zero to two months, and then, after that, from two to four months, for both males and females, there was a

difference in the other direction, a large difference in the other direction.

For males, it was about 6 grams per day, and for females, it was about 3 1/2 grams per day, and then, similarly, the growth rates are all slowing, but there's similar differences from four to six months.

So, basically, in the Iowa, there was no difference in the early period and a difference afterwards in favor of formula feeding, but in the other data, the Newfoundland data, the breast-fed infants grew faster in the first two months and then more slowly after that.

DR. GARZA: In the Icelander data, what years were these infants fed? Do these come from formulas fed in the '80s or formulas fed in--the Iowa data, I assume, were formulas in the '70s, Dr. Fomon?

DR. FOMON: They went from 1968 to 1987.

DR. GARZA: With the predominance being about equally spread throughout that period?

DR. FOMON: I don't know. There's no difference between the earlier and the later.

DR. GARZA: Dr. Sigman-Grant.

DR. SIGMAN-GRANT: I didn't catch the differences in the four to six months. Same direction as the two to four months?

DR. FRONGILLO: In both data sets, in the later period--so, in four to six months for the Roach data--there was--the growth rates were faster for the formula-fed.

The difference wasn't as great as from two to four months, but that's partly, I think, the rates are just overall lower.

DR. GARZA: Any other questions?

Part of the difficulty that we will face as we go on to the next questions is that, as we look at these growth differences, that there are other physiological differences between these groups that are difficult at least for me to interpret in that when studies had looked--compared breast- and formula-fed infants, there are differences in basal metabolic rate, for example, between the two groups before even differences in growth rates up here.

There are differences in heart rate, in temperature regulation, energy regulation.

So, there seem to be some concrete physiological differences that go along with the differences in growth that need to be borne in mind, so that whether or not one pattern is consistent with those physiological differences, whether they're adaptive or not, makes the interpretation of this data particularly vexing at times.

Are there any other questions that you all have to any of the presenters?

DR. BAKER: I'm just thinking about this. We've heard that a formula wouldn't be introduced unless it was going to be better. We don't know what better is.

We've also established that our best shot at what adequate is is growth. That sort of sums up the adequacy of a formula or breast-feeding, for that matter.

And then we're also saying we don't know what the right growth is, and certainly we don't want babies to grow any faster than formula-fed babies are now, maybe a little slower, but we've sort of gotten ourselves in a circle here, because in order to show better, you've got to measure growth, and growth, you don't know whether it's supposed to be up or down.

So, we can't prove that it's better. All we can prove is that it's the same.

DR. GARZA: That's been the view of some of the presenters. They don't necessarily have to be yours.

With that challenge from Dr. Baker, let's move on, then.

The sense I had from yesterday's discussion is that, if we look at question 4A in the abstract in terms of distinguishing values and merits of each type of reference, that there was a very clear preference that the default option ought to be concurrent controls unless

otherwise justified, that if one could justify the--not running concurrent controls, that, in fact, one could move to reference data such as either the Iowa or the CDC, NHANES, etcetera, reference data that were pretty much in the public domain, so to speak, and that only under unusual circumstances would one rely on historical data.

That was pretty much true for term infants.

For pre-term infants, the group felt that concurrent controls were necessary. We didn't see a way that one could rely on either reference data or historical controls because of the dynamic nature of the treatment of these infants and the center differences that exist.

Is that pretty much where we left the discussion?

So, if we move from there to B, which says these reference groups are based upon--please rank these reference groups based upon the ability of the respective control population to contribute to an assessment of normal physical growth in the population intended to consume the formula.

And the reason why it moves us away from the abstract is that now we're dealing with that phrase that I was pressing the group we just heard from, and earlier groups, in terms of normal physical growth and whether,

in fact, in assessing the normality of that growth, how one would do that with concurrent controls and what is that concurrent control, and we will be coming to some of that in question 6.

If you use a reference, category number two, you're faced with the same question which Dr. Baker introduced for us a little bit earlier, and if you move to historical controls, I think that's possibly the easiest, because we can pretty much, I think, from the discussion we had, say, well, that's not going to give you much help given the nature of the way we define historical controls for purposes of this discussion.

Who would like to tackle B? How would you rank these in their ability to contribute to an assessment of normal physical growth? What would be your concurrent controls?

Any takers?

DR. HEUBI: I don't think that we've actually--independent of this issue that we can't define normal physical growth, which is a real problem here.

I think we still are saddled with concurrent controls and longitudinal reference data, sort of in that order, and historical controls somewhere down the line.

I don't think we've changed--even if you change the verbiage of where you put exactly what you're comparing it to and knowing that this is impossible for

us to know what normal really is, I think that's where we are.

DR. GARZA: I'd like to challenge the group.

Is that really impossible to discuss? Can it be true that we're in the 21st century and have to turn to an agency like FDA and say, gee, a group of experts can't decide what normal physical growth is?

That is a terribly telling comment on pediatrics if it's correct.

DR. STALLINGS: I guess I'm prepared to take Dr. Garza's challenge.

I think we have to make a recommendation. That doesn't say that that will be the same recommendation in 10 years when, you know, this will need to be done again, but I think, from the pediatric point of view, from a child health and child advocacy point of view, for the purposes of the exercise, that a healthy child born to a healthy mother exclusively breast-fed for the first four months is our best guess today of what normal growth should be.

I'll put that out for discussion, in term babies.

DR. GARZA: So, in your mind, a concurrent control would be that, that in fact one would have to run a group of breast-fed infants as concurrently with

whatever you were doing and then make judgements based on those comparison.

DR. STALLINGS: Well, it's interesting, I think, in my homework last night that you sent me home to do, that that became apparent, because I changed something of my theory that I would actually be interested in knowing how it performed against the current formula, but I also wanted to know how it performed against breast-feeding, breast-fed, healthy breast-fed babies.

So, I think we're entering a time when that may be, in fact, true. I look forward to seeing the WHO data and for us to learn about that, but knowing--you know, knowing the process, that won't have any real-life impact certainly for a regulatory agency until that growth grid is out and we've all had a little bit of time to use it, and you know, the whole implementation, education, assimilation process that goes with such a major change and approach.

So, I think we've got to do something between now and then, and we may want to go back to our experts to ask, if we ask the question differently, what is the best set of data that we have for breast-fed infants in the U.S. currently existing or combinable or whatever, could we end up with something that would be a relatively robust reference, not a standard, but I don't know the

answer to that, and that might be one of the challenges if this committee or other committees works.

But I think we have to take the leap and go with the breast-fed baby as the model for normal growth.

DR. GARZA: Let me ask you two questions, Virginia.

Number one, would you then suggest to the group that, in fact, we need to have two concurrent controls--one would be whatever formula plus a second group--or that, in fact, you might use the sort of reference that you just described for the comparison or the comparator for the breast-fed group, and would an interim use of, for example, the WHO breast-fed data set that Ed described that led to the current reference and has about 200, 300 children in it from North America and north Scandinavia or a Scandinavian country--would that be a sufficient reference?

DR. STALLINGS: I would be willing to consider it.

I think what I would ask is for us to have access to the data and be walked through it, you know, in a responsible way, because it's not at a peer review stage yet.

DR. GARZA: Well, it's been published both in the Journal of Pediatrics and in the--and there is a whole booklet out by WHO --

DR. STALLINGS: Okay.

DR. GARZA: --that's out there.

DR. STALLINGS: So, I would certainly be willing to consider that, but it's clear from my last comment that I'm not fully informed.

DR. GARZA: You would consider a reference group rather than two concurring groups and someone would have to have three groups in a feeding trial.

DR. STALLINGS: Right. I would consider that.

But what I'm interested in is us having--instead of showing the growth grids that we have been using--historically, the '77 ones and now the 2000 one--I would be interested in exploring having a breast-fed cohort so that we could start to understand that.

I mean I see this as a process, certainly both for the public health interest of the children and for not wanting to take away an important product for babies that need it.

So, I'd like to learn more about that, look at the data, be walked through it.

I don't think if we're changing formulas that we could not look at them compared to this history of incrementally-improved formulas, which is what industry has done.

I just worry that with each of those steps that we've trapped ourselves into the bigger-is-better

category and that that's what we're seeing, and I think as was suggested, you know, that it may be a fundamental regulatory change, that maybe infant formula shouldn't be at, you know, .67 calories per cc, that that may not--in all total, that may not be the right thing.

I mean I don't know the answer to those things, but I think we have to be open.

DR. GARZA: Dr. Stallings has made a suggestion.

Dr. Thureen, do you want to respond to that or make a different one?

DR. THUREEN: No, I think it's the same thing, but I want to make sure that I understand you.

The current growth standard should be that of the breast-fed infant, exclusively breast-fed to four months of age. That's the standard for normal growth.

As a separate issue, what should we use for concurrent controls? For the present time, probably a concurrent group of formula-fed infants that doesn't have the modification that's being studied.

Ideally, in the future, we'd move towards the second concurrent group, that of breast-fed infants, with looking at that as a reference standard and maybe with using neuro-development, outcome, etcetera, but that's a process that would occur over time, so that there would be no change in recommendation for the current time of using concurrent controls of the same formula without the

addition but move towards, over time, having a different concurrent control group of breast-fed infants.

Is that what you said?

DR. STALLINGS: I think so. This is clearly a thought--I mean this is the part of our work that we need the dialogue for the clarity.

I am very interested in having both--when working in isolation last night, I actually came up with both concurrent control groups, a breast-fed contemporary group and the primary formula and then the formula with change, when I was looking at what would I really like to do. So, that really is an issue.

If we were to go that way, if we use the breast-fed baby as the only concurrent control group, we know we're going to open up gaps immediately, because the growth patterns aren't the same.

So, I don't have a good idea how to walk through that part.

So, there really are two questions. Is the new formula as good or better as the old formula, which is usually our question, and then, secondly, how does it compare with breast-feeding?

The challenge that I don't know yet is can we create a reference set that performs well enough that we wouldn't have to have a concurrent breast-feeding group.

So, I really offer this to begin the discussions. I'm very interested in other people's thoughts.

I do feel strongly about--that as much as we--and I know everybody in this room would want to do this, certainly protect children from unnecessary studies, I think as pediatric health advocates we also need to affirm that sometimes we do need to do studies in children and not be afraid to do the right ones. It's the balance.

So, I'm not afraid of doing more studies on more children to get the right answers.

DR. GARZA: Let me ask the group and possibly our presenters to also comment on this, those that presented yesterday.

It's my sense, as I look at the literature, that if one looks at the growth patterns of breast-fed infants, either historically--I looked at data back as early as the early 1900s and it's very sparse, but there's some there--and cross-culturally, looking at children, for example, in such places like Bangladesh to Norway, the pattern of growth is remarkably similar.

They start off at different places, obviously, so that, in fact, the children at Bangladesh may start off at minus-3, but if you plot their growth--minus-3 standard deviation--if you plot their growth against the

WHO breast-fed data set that Ed showed us yesterday, parallels it pretty--I mean just phenomenally well.

If you look at Norwegian infants, again they're much bigger at birth, they parallel it pretty well.

Has that been everyone's experience, and if true, would studying a concurrent group--would that sort of consistency make as much sense, or has it not been your experience so that, in fact, one would need a concurrent group to try to be able to overcome the sorts of biases that reference data might unintentionally create for us?

DR. STALLINGS: I'll make one comment to that, and then, really, I'm very interested in my colleagues' opinions.

I think, in North America, practitioners have been often frightened by the fall-off of breast-fed kids compared to our growth grids. So, the truth is I'm not sure many of us have really looked at that as carefully or might be able to express personal confidence.

And then you also--the people that you have around the room--often our jobs are to deal with children who have failure to thrive. So, again, you know, most of us have not been doing general pediatrics practice where we're seeing the more run-of-the-mill issues.

But the one thing that I am aware of, you know, certainly in personal friendship circles and

professionally, is until we really became aware of there is the natural slowing of growth compared to the current growth grids, that a lot of people with breast-fed babies were alarmed, and pediatricians caring for them, thinking that we weren't doing a good job.

So, I think in North America we've got an education piece that's really just sort of getting out there, and you know, the issue of growth charts and the optimal reference, if not standard, is something we've been missing for a long time.

DR. GARZA: Let me turn to the group.

Dr. Fomon?

DR. FOMON: I'd like to make a couple of comments that I think are of some practical significance with respect to using the breast-fed infant as a reference.

Number one, if we were to analyze the infant formulas on the market from 42 to 112 days, almost all of the formulas would be in non-compliance, and if we tried to develop formulas that would allow us to match the growth of the breast-fed baby, we would have to switch formulas at about 42 days.

It would be the only way to do it.

You could not go with the breast-fed babies' growth and not exceed the breast-fed babies' growth if you stayed with the same formula after 42 days.

So, there are some real practical considerations.

The other thing that I think is important in using the breast-fed baby as a reference is that most of the studies do not account for drop-outs. We account for drop-outs in formula-fed studies, but in general, most of the breast-fed studies are breast-fed babies who continue to be breast-fed for a certain period of time.

DR. GARZA: Thank you.

Dr. Clemens?

DR. CLEMENS: I'd like to pick up on a comment that Dr. Merritt made a little bit earlier today, and that is, if you were to look at all the data that the industry has collected, they, in fact, would have more data on breast-fed infants in this country than WHO has collected in total, and so, if you were to use that as a standard--and to go back to what Dr. Denne said yesterday--what is the agency going to do with those data if you don't match those particular patterns?

DR. BAKER: I've got a question. If you were to try to duplicate the growth of a breast-fed baby with your formula, then you would almost necessarily have to change the whole character of the feeding trial.

It would no longer be a growth study. You would have to include lots of things, because you're not really interested in growth at that point. What you're really

interested in is the formula supplying everything it needs.

So, you'd have to look at metabolic things, at neuro-development things, at bone accretion. You'd have to blow it open to a full study, a metabolic study, in order to do that.

DR. GARZA: Let me ask the group, because that thought was crossing my mind, as well, that the assumption that, in fact, one can look at growth in isolation of anything else fails as you try--at least it failed in my mind as I tried to go through it, because in fact, one would have to look at the composition of the formula.

One would have to look at some baseline metabolic responses, because if not, one could very easily get into a false sense of either security or insecurity by relying on any single measure for adequacy, one for which we appreciate there is some plasticity.

I can give you a recipe for a small baby. We do it in most of the world quite successfully. I can also give you a recipe for a big baby and big children. We have been doing that just as successfully for the last 15 years in this country.

So that in isolation of intake data and isolation of metabolic data, one can decide what the baseline of that information may be, but what seems to be

coming out of our discussion is that, yes, you may want more than one growth comparison, as the way Dr. Stallings described, but that those comparisons have to be interpreted in the light of additional data than just growth alone, because of that plasticity.

Is that a fair assessment of how the discussion is going, or is that unfairly characterizing the deliberation?

Dr. Denne?

DR. DENNE: If I could just maybe digress a bit, I think we're talking about or at least dancing around trying to develop a formula that makes formula-fed babies grow like breast-fed babies, and to me that's a hypothesis that needs to be tested.

I mean what we know is that formula-fed babies growing like formula-fed babies do well, and they do well in the infancy period, and as far as we know, all the way through adulthood.

Adjusting our standards to make a formula so that we match the pattern of growth of formula-fed babies and breast-fed babies assumes that we'll get a similar or better outcome, and we have no basis to make that recommendation.

It's an interesting concept, but in the absence of any information like that, I would be reluctant to change that standard.

DR. GARZA: Let me be the devil's advocate for just a bit.

Is there any other circumstance in medicine where a significant deviation from perceived normal physiology would be interpreted by default as acceptable without proving that, in fact, there were no problems, where the absence of information is sufficient, rather than the presence of information?

DR. DENNE: I think if we were starting today and all we had was breast-fed babies and we needed to construct a formula, then trying to match the pattern of breast-fed growth would be an appropriate way to go.

However, we have, you know, 50 years of formula experience that actually is reasonably--with reasonable good outcomes, again all the way to adulthood.

So, given the fact that we have that experience, it's difficult to radically change the formula in order to just match a pattern of growth, which is really all we're talking about here.

DR. GARZA: What I was trying to get us to is to the point--maybe we don't have to match it but at least be able to explain deviations from it.

DR. DENNE: I think it's certainly reasonable to compare formula-fed babies with breast-fed babies. I mean I think that's a reasonable thing to do in some sort

of academic abstract way so that we know what those differences are.

But to act on those differences, I think, is where I'm less convinced.

DR. GARZA: So, your suggestion would be what?

DR. DENNE: I guess I'm suggesting that, given the fact that we have good data on formula-fed babies and the growth of formula-fed babies over many years, that that is a reasonable approach to match changes in formulas to, rather than a standard of breast-fed.

DR. GARZA: What match would you make, then, to a--what would be the concurrent control? Would it be the Fels data that has some formula-fed infants? Would it be a historical? Would it be the NCHS, CDC?

What formula would we use as a standard to get that normal growth definition?

DR. DENNE: I guess I would use some combination of a longitudinal study, Iowa, Fels data, formula-fed infants, probably as a primary source, and probably the CDC as a second source, which obviously is a mixture, and we understand that.

DR. GARZA: And that would be sufficient without the concurrent control?

DR. DENNE: No, that's with the concurrent controls. I don't think this, by any means, replaces the need for concurrent controls.

DR. GARZA: Dr. Clemens?

DR. CLEMENS: It's interesting to note that even Dr. Fomon, just moments ago, made a comment relative to the duration of kids that were on the--in his studies, and as you look at the data that were collected in the '70s or late '60s through the data that were collected to the mid-'80s, Dr. Fomon, if I recall what you said correctly, that both kids did not differ.

That's true if you look at the data that were collected in Iowa. You could look at the data that were collected and presented and analyzed through the CDC.

Fundamentally, those kids do not differ, that if you look at the historical data that the industry has generated in over 6,000 kids, all those controls, concurrent controls, mind you, that fundamentally, those kids do not differ.

LSRO did a report just a few years and examined the nutritional requirements for kids, and if you look at those requirements, that's exactly where the industry is today.

DR. GARZA: Dr. Clemens, then explain to us the differences between the Iowa data and the Roche New Foundland data, because those two differed fundamentally in growth pattern, both on formula.

DR. CLEMENS: I can't explain that at this time.

DR. GARZA: I think it's difficult to say that these patterns have not varied, because that statement, I think, is difficult to uphold.

DR. STALLINGS: It sounds like, though, there may be another source of data that we haven't had the opportunity to see, that if industry were able to provide the primary data on the breast-fed infants, you know, and the sites, the geography, the males, females, that we might have another set of breast-fed babies collected under conditions that are common to current infant formula studies.

I'd be very interested in seeing that, and I think what we're headed towards is really what the FDA is prepared to do at this point is--I mean some of this is new analysis. I doubt all of the major companies have ever combined their data.

DR. GARZA: Dr. Stallings, how would you deal with the problem that Dr. Fomon raised, which is a very fair criticism of most breast-fed data sets that I know of, and that is that, in fact, you get terrible attrition rates, and you have a distillation that gets progressively worse.

There's only one study that I am aware of that is following all children, regardless of whether they adhere to recommendations. That was the description that Ed gave us of that WHO study, where they're following all

children to try to see whether there are differences between those that quit at three months, four months, five months, six months.

DR. STALLINGS: And I think that will be an important issue. I mean I would love to see--I mean it seems a little silly at this point to start another major breast-feeding study to answer those questions in the U.S. or in North America when we're going to have really wonderful data soon.

But that is an important question, because we know what it's going to do, is add to the variability that is artificially low in the breast-fed studies now, because it's just the compliance-committed families.

So, I mean but these are some of the kinds of things that if--you know, if we got great briefing books on those kinds of things, I think the way we should head would become apparent.

DR. GARZA: There are some studies in the literature that I'm aware of that have had 3-percent attrition rates for the first four months. I mean, so they do exist.

DR. STALLINGS: Right. So, I think that's incumbent upon us, if we want to consider going down this road, is to really look at that, because it's not something that's been done, and then to be able to start to look at what--I mean we may end up with very different

sample sizes, requirements, and things like that. It may not be as overwhelmingly impossible as it feels, you know, as we're going through some of this, and to focus on those first four months or maybe the first six months.

But I also, you know, agree with Dr. Fomon that one of the challenges as we go through this is--I mean what we now know is the nutritional needs of a baby during the first two months are different than the nutritional needs after that, and the beauty of it is the breast milk supply and composition changes with that and a little bit more than we can change a commercial product.

So, then the challenge is what are the windows that we'd need the product to have to perform well on zero to two and two to four or two to six?

So, it's, you know, a lot of things that might come out of this set of questions.

DR. GARZA: Okay.

Dr. Sigman-Grant?

DR. SIGMAN-GRANT: Just to divert the conversation just a little bit, if we look into the future at the possible ingredients that might be added to formula, we talk about the nutritional needs, and it seems that because breast-fed and formula-fed infants do grow and thrive, that the nutritional needs are met.

Yet, we've been hinting upon the metabolic changes or differences that might exist, which may or may not be reflected by growth, but if some of the newer ingredients that might be added to formula may be added because of presence, say, in breast milk, because breast milk is the standard, does that put a different light and sort of support the need for a concurrent breast-fed group in the study, because that might be what might be coming down in the future, some of those bio-active or other growth substances that are in breast milk.

I mean we're trying to set some standards for the future.

DR. GARZA: All right.

I think my read is that we've come to some agreement on 4. Let me see if I'm not being overly optimistic.

We've summarized part A, so we can leave that alone.

In terms of B, the group still feels that, in fact, longitudinal concurrent controls of a formula plus--minus whatever is being tested is going to be needed under most circumstances, that we recognize there may be some--I think it was Dr. Baker that described it.

For example, if you're doing a series of studies very close to each other, that they're variations on the same theme, but in fact, one might be able to rely on one

concurrent control group for multiple studies, that it's foreseeable that that would work, that, in fact, there should be a comparison in addition to that with some reference source for the breast-fed infant to try to understand what those deviations are from that growth, that there may be instances of the type that Dr. Sigman-Grant described where you may want to run a concurrent control but that we don't envision that necessarily being always the case, but at the very least that there ought be some reference data set that one ought to be able to make that second comparison with the breast-fed population and to be able to identify reasons for the deviation, that in fact it may be expected based on historical growth patterns from other formulas that this is not unusual or that, in fact, it was to be expected because of the nature of the change, but that there ought to be some explanatory information that comes along with that comparison, but that generally, then, we would keep the ranking pretty much the way we described for A, that these would be used to assess normal growth in the way that I've just described, and so that we've done C in terms of defining the role of that reference group, as well.

So, is that a reasonable summary of 4? All right. Then, if it is, let's take a short break of five minutes to get your coffee, bring it back to the table.

I have to ask you to bring it back, because we've got to go through 5, 6, and 7, and we may not make it, folks.

[Recess.]

DR. GARZA: All right. So, we're going to go on to number 5, and that's asking us two questions.

For the purpose of evaluating normal physical growth--that's our favorite phrase again--of infants new formulas, what criteria should appropriate infant growth reference groups meet, each or selectively, in terms of feeding history, gestational age at birth, sex, racial background, socio-economic status, etcetera, in comparison to the experimental or study population, as opposed to perhaps the reference, and in comparison to the population intended to consume the formula?

I thought the second was surprising, but not so when you stop to think that, at our last meeting, we discussed the fact that term infants, for example, might be used--term data might be used to justify pre-term feeding, and so, that didn't seem so--such a disconnect once I thought about that.

So, in comparison, then, I guess, what similarities exist between the study and the control populations, is the way I interpret the first bullet, or a reference group, if you're using one, or a historical group, if you're using a historical group.

Now, we might wish to differentiate. For example, if you're doing a concurrent control, then obviously the idea would be a randomized, so that they're going to be the same if you randomly assign them.

That would be the intention of that design, at any rate.

Once one gets away from that, then there are criteria that you would have to think about in making that match, because you're no longer dealing with a randomized assignment.

So, I think the first one is easy, unless anyone would take exception to that.

Moving past that easy one, then I'll turn to the group and ask you to address the difficult one.

DR. ANDERSON: I think we want to re-emphasize how important we think it is that, in settings where a comparison is thought required, that it ought to be done through a randomized trial.

Having said that--and as I think our recommendations from the last meeting implied, the randomized trial ought to be done optimally in the population designed to consume the formula, or there ought to be a compelling argument that the answer that one gets in a different population is the same as one that one would have gotten if one had done it in the population intended to consume the formula.

I mean after that, I think the--any other approach is sub-optimal but that the focus ought to be on the kinds of characteristics that we recognize from both randomized and follow-up studies predict for the type of pattern of growth that one observes.

So, from the discussions here, it seems clear that gestational age at birth has a major impact, and to the extent that there are other factors that are readily measured that are known to be strong predictors, that it would be incumbent on those submitting such information to be able to demonstrate that the results that are observed, either--for instance, if they were largely similar, that the similarities are not as a result of underlying differences and predictors of growth that, if they were adjusted for, would lead to very different observed growth patterns.

DR. GARZA: Based on what we've heard, then, one would definitely want to see a match on sex, because of differences between boys and girls.

One would want to see a match on gestational age, for reasons that we've discussed.

Health--general health standards would be a third that we talked about, that you couldn't necessarily extrapolate from one healthy population to unhealthy populations, or conversely, and we had detailed discussions of that point at the last meeting.

Less clear are feeding history. For example, if, in fact, one was comparing two formulas and one formula group was fed human milk or some other formula in the early period to a greater degree than the concurrent or comparator group, would that present a problem?

I mean how closely do you want--do you think that one ought to look for a match with feeding history? I mean that's something that has come up.

In terms of racial background, it's tough for me to make a point for that one.

Socio-economic status--tough for me to make a point on that one either. I mean all kids ought to grow--I'll use the phrase "normally," whether they're rich or poor. In a society such as ours, I don't see that that's relevant, necessarily.

DR. SIGMAN-GRANT: The feeding history--you just mentioned formula or breast-fed, but I would think you would want to match on introduction of solids and other weaning and complementary foods, because we haven't talked about that, but some of the data from some of the years, complementary foods were introduced very, very early, and that may have been different for breast-fed and formula-fed babies.

So, I think you would want that in the study.

DR. GARZA: Complementary feeding history?

Other matches?

DR. DOWNER: I was thinking about socio-economic on the grounds that, if you don't have money to purchase formula and you're not breast-feeding, that will definitely impact.

I understand that the goal is, regardless of your socio-economic status, to make sure that you have the best outcome possible, but if we're looking at matching, I think that is very important to look at.

DR. GARZA: Okay. I was working under the assumption that, if you were doing a growth study, then those factors in terms of accessibility would be controlled. Perhaps that's too much of an assumption.

Do you feel that SES matches would be necessary, Dr. Heubi?

DR. HEUBI: That wasn't what I was going to comment on.

DR. GARZA: All right. Well, let's get done with this one, then, on SES.

DR. HEUBI: I will comment on it.

I do think it's probably important to match as much as we possibly can on SES, although I sense that, after having participated in some of these trials, that we're basically doing that in general, because in most cases, you're excluding children who are in the WIC programs because there's no real incentive for them to participate in these studies.

DR. GARZA: What is the biological proxy that we're using or what is the proxy for SES, then, because I'm trying to understand the biological reason why you'd want to control for SES if you're doing a growth comparison between two formulas.

Kids that are poor don't inherently grow slower. I mean they grow slower because they don't get food.

DR. HEUBI: I'll tell you what my first-blush response to that is, is that there are so many other extenuating circumstances in those households that may somehow impair their growth and may not make them --

DR. GARZA: Dr. Clemens?

DR. CLEMENS: Actually, demographically, in the control, as well as in the study population groups, the intent for the industry is to be absolutely identical, and that's indicated in the protocol, including the SES.

Breast-fed kids are self-select, so it's difficult to match SES, and it's difficult to match some of the other parameters. It's difficult to match the in-house situations as well, as you probably have experienced.

DR. GARZA: All right. So, one would then look at SES but look at particular variables, I would imagine, like maternal education, birth weight, all the various things that you think would be impacted to make sure that, in fact--that's the sense of the group.

DR. CLEMENS: That's correct. We do that already. That's indicated in the protocol.

DR. GARZA: Dr. Heubi?

DR. HEUBI: I think it's probably not totally appropriate to be over prescriptive about what their antecedent breast-feeding or formula history was before they are enrolled.

It depends upon when you want them to be enrolled for the beginning of the trial that would determine whether you would restrict what their previous feeding history was, and that's a piece that I don't think we've really addressed.

I know there's been discussion about trying to enroll age 14 days, and Dr. Fomon talked about at age 28 days, and I think that's a piece that ends up being fairly important, about when you enroll your subjects in terms of what their antecedent feeding history truly is.

Certainly in the circumstance where you were studying a soy formula, you wouldn't suggest that they be switched from a cow's milk-based formula to soy, and similarly, you wouldn't suggest that a breast-fed baby would be switched to formula to participate in the study.

DR. GARZA: So, how do we deal with--what is the match between feeding history--it would just be dependent upon the nature of the study, so it's very difficult for the group to make a generic comment, other than that you

ought to think about it. Is that what the group is saying?

DR. STALLINGS: Not to directly answer that, but I think one of the groups that we have--often, many of our studies are designed to keep people exclusively formula-fed or exclusively breast-fed when, in fact, in practice, the third group, the mixed feeding children, are really very common.

So, I just bring that up as--that's something that I think we need to incorporate, because that really--when you talk about the environment that you're really going to use the formulas, as we get more and more successful for breast-feeding for the first number of weeks or months or however, the other type of complementary feeding, when you need the formulas to continue that cycle. So, I just wanted to bring that out, and in fact, that was part of the discussion at break.

I think it's beyond what we can do in this setting to really keep detailed history of complementary feeding.

We might be able to say first initiation, because it just gives you a time point, and I think that's probably accurate, but--so, my sense is I really would not deal much with complementary feeding, other than maybe record it.

The feeding history, I think, will be a moot point, because I think we're going to need to enroll them by eight days or 14 days, and then the rest really goes from the protocol inclusion or exclusion criteria.

DR. GARZA: Dr. Sigman-Grant, do you want to comment to that?

DR. SIGMAN-GRANT: From the practical standpoint, I really think you need to account for complementary feeding.

It's so variable. If you're not in a hospital setting, the time of introduction of cereal varies from--even now--from a couple of weeks to six months.

So, it's so variable, I think you at least have to account for it, maybe not measure it but certainly account for it.

DR. GARZA: You would agree that the only thing that you see as critical is the age at introduction, not necessarily keeping--or collecting additional information for the amount of complementary feeding that occurs, how frequent it is, whether it increases over the time of the study, but if you knew, gee, they started at one month or two months or four months, that would be sufficient, because I think that's what Dr. Stallings said, that it's the age of introduction. Beyond that, it really gets to be impractical.

DR. SIGMAN-GRANT: If you want a true picture of growth, I think you need to look at the progression. So, someone who starts complementary feeding early tends to progress, so the child gets more and more and more, and that might impact the growth study and how much actual formula they're consuming.

DR. CLEMENS: Actually, if you look at the protocol, first of all, on enrollment, we do examine whether breast-fed or formula-fed, they're not to be exclusively formula-fed, because we do note there is a difference at that point.

Secondly, all complementary feeds are, in fact, monitored on a regular basis. There is part of the form to examine all of that issue, and it's part of the compliance.

If, in the estimation of the investigators at hand or the research investigators, in fact, that the complementary feeds are out of bounds, for whatever reason, then, in fact, those individuals are out of compliance and discontinued.

DR. GARZA: So, you're suggesting that ought to be made mandatory, that the FDA ought to require that information, rather than just receive it, because it's supplied.

DR. CLEMENS: We already provide the information. In general, the industry provides that kind of information.

DR. GARZA: But you think it ought to be required that everybody supply that information. Is that what you're saying?

DR. CLEMENS: We can work with that.

DR. GARZA: The reason I'm asking is, if there is a new manufacturer that's not part of the Infant Formula Council and they choose not to, right now there's nothing that requires it.

DR. CLEMENS: That's right. That's not required.

DR. GARZA: And I was asking whether you felt it should be required.

DR. CLEMENS: It should be required, and we do provide those kinds of data.

DR. GARZA: Okay.

Any other comments on that?

[No response.]

DR. GARZA: All right.

So, in comparison to the population intended to consume the formula, how much of a match should there be between your test population--the example that we've dealt with in the past is, can you study term infants and then make inferences to pre-term?

Are there other instances where you think that, in fact, if it's studied, for example, in six-to-12-month-old children, should it be used at one to six months?

We had some discussion as to how the nutritional requirements were quite different between infants the first three months and the last three months of infancy.

So, that's another example, I think, that we heard about where there should be a match between the study population and the population for whom the formula is intended.

Obviously, boys and girls, because it's intended to feed both sexes.

Those are the easy ones.

Are there other matches that you feel ought to be made?

DR. DOWNER: Also mention the gestational age.

DR. GARZA: Okay.

DR. DOWNER: And general health.

DR. GARZA: All right.

DR. BAKER: I would say that this--if I'm reading this question right, it's driven by science, and you match you control group to your trial group as closely as possible, and if you want to make inferences on some other group, that's up to you to prove that

that's okay, but you don't match your control group to some other group.

DR. GARZA: It has to do with a study group, I think.

As I'm reading the question, they're asking, if you set up a study group, how closely does that study group have to conform to the intended population, so that the external validity issue is the issue that they're getting at? I think that's an external validity issue.

DR. DENNE: I just was going to say I think, you know, at least in some sense, this ought to reflect the population of the United States and that, although that's probably impossible in a relatively small study, it shouldn't exclusively focus on a specific socio-economic group. It shouldn't specifically exclude--explicitly just be white or black. It should be relatively representative.

At least that's the way I read the intent of the question.

DR. GARZA: Dr. Kuzminski?

MR. KUZMINSKI: My logic takes me just to a very brief answer, and the answer it is very closely, because under the criteria, I would have to defer to the medical expertise, but if the change is being contemplated against an existing formula that's out there in the marketplace and I would think a manufacturer would want

to know how that change is going to affect the market for that existing product.

So, whatever medical parameters can be put into the study design are the appropriate ones, they should be included, but in terms of the context of the question, how closely should the population intended to consume the formula be represented in the study, I think very closely.

DR. GARZA: I think that's the sense. I don't think I could summarize the sense of the group any better.

And before I forget, Dr. Kuzminski and I had a discussion during the break, and I want to make sure that--I thought we weren't in disagreement and that we had not shut the door on the use of historical controls or term infant studies in question 4.

We listed it last but recognize that there would be instances where that would be appropriate but that that would have to be justified, that in fact, because it was the lowest--the least well-received or ranked last, that, in fact, it couldn't be used without some justification and that we didn't see that case with pre-terms but with term infants that that might be possible.

Dr. Anderson?

DR. ANDERSON: I think relative to the present question, to the extent that the study population

differed from the population that intended to consume the formula, it would be incumbent on the manufacturer to demonstrate that there was no reason to suggest that the findings of the study could not be directly applied to the population for which the formula was intended.

DR. GARZA: So, you'd like them to address the external validity of their data.

Okay. Well, we've dealt with 5.

Dr. Heubi?

DR. HEUBI: Just as a point of clarification, does the FDA require the same kind of demographics as the other PHS agencies for clinical trials?

Do they require Hispanics and African-Americans?

DR. GARZA: The answer was no, since the record shows the staff shaking their head, and obviously, the sense of the committee was that, in fact, those groups ought to be representative in the sense that Dr. Denne described. I didn't hear any objections to that.

It's an important point. I think not many of us have been involved in trials.

I remember being involved in one trial where we were told that they couldn't find African-Americans, and the study was being done in Manhattan, which I thought was amazing. I offered to give them a tour of the city.

DR. WALKER: You used the word "require." I think it's important to remember that this is a

notification process, not an approval process, and we're under very different regulations than you would be in a drug approval process.

DR. GARZA: Thank you for that clarification. That's important.

DR. HEUBI: All I can say is we're used to being hammered with this at the NIH.

DR. GARZA: All right. Well, let's move on to number 6, and I'm actually more optimistic. I thought this was going to take more time, but much of our discussion for question 4, I think, might help us deal with this one.

So, listed below are examples of control feedings or clinical comparators, and then you have six bullets.

You may have other comparators that you would like to present to the group.

We're being asked what are the most distinguishing values and merits of each of these types of comparisons in infant study test formula versus a comparative feeding for assessing normal physical growth, and there again, we have that phrase of "normal physical growth" coming back to us.

So, you've got these six bullets. I'll read only the first two: a current infant formula plus a new

ingredient, a current infant formula, obviously, with out that new ingredient, and human milk.

So, those are three groups.

We've talked a little bit about how one might use those three groups in our discussions of question 5.

A second was only the first two groups that I identified, and then there are various permutations through the six bullets which we don't have to read.

So, who would like to tackle A? And here again, we might want to take only those two or three that would be of most value, perhaps have some that are moderate value, and those that you would never suggest that anybody even consider doing.

Dr. Anderson?

DR. ANDERSON: Well, I'll take a shot at this, because I think I'm likely to be somewhat controversial.

I think that the most useful of these is the second one, which is the test formula versus the formula without the new ingredient.

In the context of assessing whether a new infant formula is appropriate for marketing, I personally don't think a concurrent cohort of breast-fed infants is relevant, although I do agree that an assessment of the growth data to some reference may provide useful information.

There's an issue that hasn't been discussed all that greatly here but which I want to raise briefly, is that we've heard this morning that there's a great deal of historical data available, and I must say that my enthusiasm about the use of historical data would depend greatly upon what those data look like.

So, for instance, if, of the 60 trials we heard about this morning, their observed growth patterns for marketed formulas were all extremely similar, so that the variation from one study to the other was minuscule, and one came with a single cohort of individuals fed a new infant formula which tracked exactly as the others did, my enthusiasm for that being sufficient information to conclude that it promoted growth consistent with that seen with contemporary infant formula would be high.

On the other hand, if the variation from formula to formula was quite large, then my enthusiasm for using the historical information would be diminished, and as my enthusiasm for tests in populations which are not those intended for use is low.

The idea of testing infant formula plus a new ingredient so that that new ingredient could be added to some different matrix or some different formula would also be low.

DR. THUREEN: The second bullet is sort of number one in preference. Then, good historical controls

would be number two, then? Or didn't you even go that far? Bad historical controls would be at the bottom.

DR. ANDERSON: If forced to rate the options, I certainly have no objection to the collection of information from breast-fed infants at the same time the study is conducted, but I personally don't think that the information is terribly useful for the purpose that the study is being conducted.

So, having said that, the second bullet would be my first and very much favored choice of the ones available.

DR. GARZA: What if one were to modify the first bullet to indicate the use of reference data of the type that we discussed in question 5? Would that be preferable to bullet two?

DR. ANDERSON: Then it would come very closely beyond bullet two, in my way of thinking.

DR. GARZA: That would be your favored bullet and having all three?

DR. ANDERSON: No. Two would be first, and one would be very closely second.

DR. GARZA: Okay.

So, you would see the comparison with a reference of breast-fed children as being less valuable than just the comparison between the formula and the formula plus ingredient.

DR. ANDERSON: Absolutely. So, three would be very much below--in fact, I would have three probably below four and five.

DR. GARZA: I was suggesting that the first bullet would be modified to not having concurrent children but a reference.

DR. ANDERSON: Right.

DR. GARZA: And then bullet two would be just as it is there, with children being--a breast-fed reference, I'm sorry. And then number three would be a concurrent infant formula plus a new ingredient with actually recruiting breast-fed children, so that there would be a difference between bullet one and three.

So, with that modification, it would be bullet two that would be your favorite.

DR. ANDERSON: If I understood what you said, in the first line, the breast milk was meant to mean some reference, then I personally would find one and two essentially identical.

DR. GARZA: Okay.

DR. ANDERSON: Three, where there was information on infant formula plus a new ingredient and information on either a concurrent breast-fed group or a reference would be very much less, because there is no either randomized comparison group with the infant formula without the new ingredient or some reference to

the expectations for infant growth when fed what's known to be appropriate infant formula, so that, to the extent that the references and the historical data provide a clear sense of what the expectation would be for the outcome when infants are fed an appropriately formulated infant formula, those then would become sort of second tier from the first and the second.

DR. GARZA: Okay.

Dr. Sigman-Grant?

DR. SIGMAN-GRANT: I'll take a different approach and go from bottom up.

Because of the difference in formula matrix, the last one, the infant formula plus the new ingredient, versus any of the others, I think that should probably be very justified, because like we heard yesterday, the composition and the batching and the process may vary amongst formula companies, and therefore, needs to be tested within each formula.

Currently, I think that, given the data and the status today, just having number three, current infant formula plus a new ingredient, versus breast milk, would not be appropriate right now, that that would not serve as a good comparison.

DR. GARZA: Okay.

DR. SIGMAN-GRANT: The current versus the historical data or the current plus the new ingredient

versus the reference data--if you look at that, I think comparing it to a longitudinal historical data would be preferable over cross-sectional.

So, in other words, the Iowa-Fels would be preferred over, say, the CDC's.

I have a toss-up between the first two.

I think if you're going to have a current formula and adding a new ingredient, you must compare it a historical--the formula without the new ingredient. You just have to. It wouldn't be appropriate not to.

I would prefer to see a breast-fed cohort or comparison to a breast-fed reference standard, so that somehow we can start establishing that comparison, because I think we've gone around and around and around, and we need to at least start addressing it.

So, this might be a good point in time to recommend that we start collecting or compare it to breast-fed babies.

DR. GARZA: Is there anyone that wishes to disagree with that general ranking? I'm not too worried about those that we've ranked at the very end, because I don't think we would be recommending those to FDA anyway.

Dr. Stallings?

DR. STALLINGS: I tried to make myself put them into two categories to start, I mean sort of rare to no, that they shouldn't be used, and this is recognizing that

we are shifting, you know, the concept of normal physical growth and that the work of the first day and some of the others have been that we are concerned about both failure to thrive and over-nutrition.

So, my rare to no's would be the last one, would be number five, which is just the new product versus only reference data. It would be number four, which is sort of what would be the new product versus other reference data, and when I did that, I also began to feel that the number two, which is new product versus old product, with no comparison to breast-feeding, would also be rare to no.

So, that leaves me the number one, which is the new product, the old product, and reference data for breast-feeding, or number three, which is the new product--no, sorry--number three would not be good, because it doesn't contain the old product.

So, I really--over the process, it really is about old product, new product, and either breast-fed babies as a concurrent or breast--an adequate breast-fed reference, which we know we need to work on some more, but those would be the two really viable options.

DR. GARZA: Dr. Baker.

DR. BAKER: I agree--I would list number one as first, but I think it's--there is also some use in including other reference standards besides the breast-

fed baby to avoid formula drift, to make sure that you're not going in one direction all the time.

So, I think some other references might be appropriate, as well, and as I understand it, that's not really that hard to do, so we're not asking a whole lot.

DR. GARZA: Is there a reference that you've heard that you would recommend?

DR. BAKER: As I understand it, I think that the Fels data, the longitudinal data, would be preferable to the NCS data.

DR. GARZA: Okay.

Dr. Clemens.

DR. CLEMENS: Thank you very much for the opportunity to speak.

Just to make a comment on the matrix, which we don't have any food scientists in the group, I think Dr. Benton yesterday commented on batching--Madeleine, you made a comment, as well--historically that you look at the worst case scenario, and that is you look at liquid processing, usually receives the greatest amount of thermal impact, if you will.

That is typically the product that is used for clinical trials, to look at protein digestibility, matrix. You could look at available leucine, reaction products, all those kinds of things.

That is considered, if you will, the worst case scenario.

That is the product which we evaluate, and that is the matrix which we assess at clinical trials.

Based on our clinical experience, based on our food science knowledge, and based on our own theory and understanding of food processing, food chemistry, we realize that, when you spray-dry a product, it's not nearly as severe, so hence we do not do clinical trials on products, some logistical things, as well.

Secondly, I think it was Dr. Merritt this morning, as well as Dr. Vanderhoof and Dr. Saavedra, indicated typically we will conduct clinical trials using the--if you will--the new product, if you will, as well as the old product or the product currently on the U.S. market.

However, there are cases, a case-by-case situation, where we, in fact, can provide cohort data that we don't run a concurrent control.

Also, we have--in each case, we have data compared usually to the Fels, NCHS, or we can, in fact, today compare it to the CDC data.

So, all those are really quite easily done.

I just wanted to reiterate, typically we conduct trials, current infant formula, as well as the new

product, as well as with the option of providing cohort data, which are from clinical trials run in the past.

DR. GARZA: Okay.

Dr. Briley?

DR. BRILEY: I would go with the first one as number one, and obviously, we have to have the current infant formula with the new ingredient, as opposed to testing against the current formula, to see what the differences were.

I still think, unless we get reference data on the breast cohort, we need to start doing that, and maybe we can get it as a reference. Maybe we just have to start collecting it. But I think we need to be looking at that.

DR. GARZA: But you would be willing to accept both, either if FDA looked at a reference data set or a data set they could use to compare breast-fed infants' growth patterns with these others, that would be sufficient, or would you conclude that no, they have to have a concurring group of breast-fed infants studied, in addition to the other two?

DR. BRILEY: That's a pretty hard thing to call in the sense that the reference data--I guess I'd want to see it to see how well it came along and how old it was.

There are a lot of factors in breast-feeding that we can't address here that make a great deal of

difference, and so, I'm going to opt on that one to say reference data for now, until we see it, and then go from there to make a decision later.

If it's good enough, then fine. If it's not, then let's go back and get it.

DR. GARZA: Okay.

Dr. Thureen?

DR. THUREEN: Well, I don't think I fundamentally disagree from anybody. I think that the second bullet is probably the most practical, current formula versus new ingredient, and running a concurrent study.

If you've got the reference data from breast milk, I think that's great. I wouldn't go out and initiate a new study just to prove that the new formula is better compared to breast milk. So, one and two almost become equal if you've got the data.

Close behind that would be great historical controls. That would be number three, but it could almost equal the other two if you had really good, nearly concurrent data, and then farther down would be the reference group, but I don't think there's a strong indication right now for doing a breast-fed concurrent control with a new formula.

DR. GARZA: Dr. Denne?

DR. DENNE: In the interests of time, I would concur.

DR. GARZA: Dr. Kuzminski?

MR. KUZMINSKI: I concur exactly with Dr. Thureen.

DR. GARZA: Dr. Stallings?

DR. STALLINGS: I think what Dr. Baker said was very important, and I realized if I were sitting on the other side of the table, I would want this information.

So, all of the studies, I think, still would be reported compared to the CDC data, because we're going to need to know that. All studies would have the new ingredient formula, because that's why we're doing it.

Then studies would either have a concurrent old formula group or very recent, very comparable historical data, like we did it last year, very tight, and then the breast-feeding control group is either concurrent breast-feeding group or solid reference data.

So, I think there really are four components to what the regulatory agency should be evaluating.

DR. GARZA: One of the things that I heard--perhaps I heard incorrectly--from Dr. Baker was that a longitudinal component would be important.

That's missing in the CDC. Would you prefer the Fels, Iowa data that, in fact, at least is based on a

longitudinal design, as opposed to the CDC? Because I thought that's what he had said.

DR. STALLINGS: I think you're right. If it were my job to make a decision whether it was safe or not and all of these things are really just data presentation, then Fels, Iowa would be, really a fifth component.

Then you would have the longitudinal data. You would have the data that all of us see on a daily basis, what is the growth grid that we use.

So, then you've basically--no matter what the question was, you've got all of this stuff in front of you, and those are not difficult things to provide. Those are just running it on a different growth grid.

But I think, then, that puts the regulatory agency in an opportunity to see it and to be able to answer all the questions, and certainly industry is going to want to know all of that anyway.

I don't think any of this would be things that they would not have explored.

DR. GARZA: Before I turn to Dr. Clemens, is there any voting member that wants to modify what Virginia just said? What she's saying is she feels that having two concurrent feeding groups, a current formula group and a current formula plus new ingredient group,

that one would then take that data and compare it to at least three different growth patterns.

One pattern would be the breast-fed group, wherever that data may come from, a second pattern would be the Iowa, Fels longitudinal growth pattern, and a third would be the CDC growth grid, but that one would want to see how growth compared across those different reference data sets and explain deviations from it, either positive or negative.

Dr. Kuzminski, is that what you said?

MR. KUZMINSKI: I think that's very thorough, extremely thorough.

DR. GARZA: Is that a code word for not necessary?

MR. KUZMINSKI: I think I anecdotally, to a colleague here, used the term "is that overkill?"

DR. GARZA: Dr. Briley?

DR. BRILEY: But I would argue you would have those data.

They're already there. They're in the computer, and each time you did a new formula, you would only have to compare it to that and explain what's going on.

I mean it's not like that you have to go back and collect it again. There would be a little bit start-up, maybe. Maybe not. I don't know what they keep now.

DR. BAKER: I'd agree. I don't think that's overkill.

We're not really asking to do another study, another group. We're just asking for comparative data that's already there.

So, it's not a--that's not a big deal, I don't believe.

DR. GARZA: Let me ask Dr. Fomon to comment on this discussion.

DR. FOMON: Thank you. I know I'm not allowed to comment. I appreciate it.

I just wanted to make the correction that everyone has been speaking on longitudinal data about the Iowa, Fels data. The Iowa, Fels data as presented are not relevant to this discussion. It's the Iowa data.

The Iowa, Fels data start at birth, which are reported weights and are reported for birth to one month, birth to two months, one month to two months, one month to three months, and so forth. What you need for formula comparison is eight or 14 or 28 days to some later time.

It's the Iowa data, not the Iowa, Fels data.

DR. GARZA: Thank you very much for that.

Dr. Clemens?

DR. CLEMENS: Your earlier comment--compared to the various groups--the question, if you collect data from breast-fed kids, how do you compare--what are the

significance of those comparisons? We don't know that. I think we're much too early into that.

Maybe this is an opportunity, frankly, to look at a research opportunity and to explore those particular comparisons for future application. From a regulatory perspective, it seems in what we've discussed so far, the terms concurrent controls, historical controls, as well as the Iowa data, would seem to be quite appropriate, but I think we're much too early in understanding the significance and comparison and impact of breast-fed and breast milk to make that comparison from a regulatory perspective.

DR. GARZA: I don't think anyone suggested that there be concurrent breast-fed data collected but that, in fact, since everyone we heard from industry indicated they didn't know what a normal pattern was, then, indeed, making those comparisons seems to make sense.

DR. CLEMENS: What is the significance of that pattern?

DR. GARZA: If you deviate from it, I would imagine you'd have to describe why you thought you deviated.

If, in fact, you deviate--let's assume that you've got two formulas and one formula deviates, it goes up or down. Is it good or bad? From the old formula.

DR. CLEMENS: From the old formula, it's one thing, but deviating from breast-fed is another issue.

DR. GARZA: What will it mean if it goes up or down from the old formula?

DR. CLEMENS: We can explain those deviations. We just can't explain the deviations we see with breast-fed kids.

DR. GARZA: I don't know.

Is that the sense of the group and, in fact, making that comparison makes absolutely no sense?

Mr. Anderson?

DR. ANDERSON: I don't think that it makes no sense, but I do think that the--for the purposes of this discussion, the relevant comparisons are not to the standard, but to the extent that a new formula differs in substantive ways from old formulas in the ways that they deviate from breast-feeding, and so, my personal view is that these references are useful not for the absolute comparisons but for their usefulness as a reference to compare new formulas to old formulas.

If, for instance--and new formula showed note differences in a prospective control group, and yet one found differences to the standard of, say, twice the increase in weight per day based on the breast-fed standard, then it seems to me incumbent that that be explained in some way.

DR. GARZA: How would you avoid formula drift of the type we've heard is possible if the only two comparisons we make is only with the new ingredient formula, so that you could always be drifting in one direction without making a comparison to one or the other?

If we just do bullet two, how do you avoid drift?

DR. ANDERSON: That's why I thought--sorry, I wasn't clear--that the standards would be important as a reference to which one could compare formulas.

I mean on that basis, you could observe drift, that curves were moving away from the 50th percentile, for instance, or that there were substantial deviations being observed from a breast-milk standard--sorry--reference.

DR. GARZA: Okay.

So, you still think that a reference--you were not in agreement with Dr. Clemens, then, or you were? I wasn't clear. Because he thought that all you needed was just bullet two, that doing the third was really not going to provide any additional information, as I understood his comment.

DR. ANDERSON: I'll let him decide whether we're in general disagreement or agreement.

The references are--my sense is the references are useful because they're references and that the useful comparisons are not a formula to the reference, because I'm not sure what that means, but a new formula to other formulas based on using the reference, because that provides information about how a new formula might--or a series of new formulas might deviate from where we have been in the past or recognize that a new formula was substantially different in some way to some reference, and in that setting, it would be incumbent to attempt to explain what those differences were.

DR. GARZA: Dr. Stallings?

DR. STALLINGS: There's some interesting potential new scenarios here.

If we're comparing a new to an old formula, a new ingredient, and now the growth is whatever the standard is, the 3 grams a day, 2 grams a day, now the growth pattern that's demonstrated is actually slower or less than the old formula but still significantly better than breast-feeding, then we may have a chance to make a different kind of decision, which is I think the regulatory agency's been in a position where it had to be comparable or better, and then make a judgement decision that we actually could have formulas that are providing adequate nutrition that don't sustain growth only at a higher level.

And that might be an interesting way to start dealing with some of the things that we have probably out of, you know, the last 10 or 15 product improvements.

So, I think this--you know, I don't think it's going to be easy, but I think it does open the possibility that we start to have--and especially with this--we've gone with the incremental data analyses, the male/female questions, and the, you know, early enrollments and looking at the first 42 days and that sort of thing.

We may actually really be able to tell things in a different way, but I think one of the things that might happen is industry might come with a formula that they believe is completely adequate from its composition and from its manufacturing and it shows growth patterns somewhere the old product and breast-feeding.

And with that, you know--and again, remembering this isn't pre-approval in the sense of a drug, that they could say, well, you know, we think we're still right on the nose, that this is a good product for all the background physical chemistry and food science and nutrient content and bio-availability, we think we've got a good product, and because it doesn't make it grow better than the last one, we are still interested in marketing it, because we think we're where we want to be.

So, I just wanted to bring that up. When we make it a two-tail test, I mean there are some things that even in the inadequate growth, if we have had product drift over the last 10 or 15 years, this might be an opportunity to start to understand that and potential next steps.

DR. GARZA: We now have three different scenarios.

One is that, in fact, we have a comparison of the two formulas plus the three references we described--the CDC, the Iowa, and the WHO breast-fed data set, for example, as a breast-fed group--a second that says no, that really is overkill, let's just do the two formula groups and one of those three but not necessarily all three, and--well, possibly two more--a third that says no, let's just do the two formula groups and a non-breast-fed reference, because we really don't know much about what breast-feeding will tell you, or a fourth that says no, let's just compare the two formula groups, because that's really what--where our interest lies, just in that comparison, as the top.

Now, that doesn't discount that you might want to do any of the other three, but in terms of a recommendation that that's all that we would see as absolutely essential.

Now, I think I identified all four positions.

Let me go around the room and try to get a sense of which among those four--and I'll say them again.

I'll just use the code "two formulas," and we'll know what that means, all right?

Two formulas plus three references--and you all know what the three references are.

The second is two formulas plus only a non-breast-fed reference.

The third is two formulas plus only a breast-fed reference.

And the fourth is only two formulas.

Now, notice that I left out two formulas plus a concurrent breast-feeding group. That was also discussed, but I didn't hear much enthusiasm for saying let's get it on the table. If people want to do it, we wouldn't object, but those were the four that most individuals spoke to.

So, let me go around and ask you to identify your top two choices and see if we can get a consensus from that as to which one would be--whether we could agree on one.

Who wants to start?

DR. MOYER-MILEUR: I think that since the data is available, I am most comfortable with number one and then would accept number three, as well, and again, number two makes me nervous because of the potential for

drift by constantly comparing formula against formula and not--and I guess I just need to make this comment, that if formula manufacturers are using breast milk as their model, then why would not the growth of an exclusively breast-fed infant be your standard? I guess I'm confused as a clinician.

DR. GARZA: I think that's a rhetorical question.

Dr. Sigman-Grant?

DR. SIGMAN-GRANT: Ditto. How's that?

DR. GARZA: Very nice. One and three, with one being your top choice.

DR. SIGMAN-GRANT: Yes. And I would exclude four.

DR. GARZA: And you would exclude four. All right.

DR. DOWNER: I think research is really to fill in the gaps in knowledge and also to validate earlier research.

Based on that, I choose four. That would be my first choice.

DR. GARZA: Why would you prefer that to either one or three?

DR. DOWNER: I think if we're looking at a current infant formula and a new ingredient, look at what

the research--the new research that we're looking at and do the comparisons within the group.

I think it would be helpful to have other data with which to compare and to contrast, you know, the new information with, and that is why I say, from the sublime to the ridiculous, perhaps, looking at the reference, one, because it's already there.

But I'd like to just look at the essential research, the new formula versus the old, and see what we're looking at, just get into the meat of it.

DR. GARZA: Dr. Anderson?

DR. ANDERSON: I would choose either two or three, and that's because both of those provide some reference upon which to make comparisons among formulas.

DR. GARZA: Would you rank them for us?

DR. ANDERSON: They're the same to me.

DR. GARZA: Dr. Heubi?

DR. HEUBI: I would choose one as my first and three as my second and probably not four.

DR. GARZA: All right.

DR. HEUBI: Because I think that there needs to be some comparison to a standard, and I'm not entirely certain that I'm real enthusiastic about the CDC standard, but I certainly believe that there should be comparison to standards, including a breast-fed reference.

DR. STALLINGS: One and one.

[Laughter.]

DR. STALLINGS: You know, I think just from what I would like to see to be able to evaluate it, but one is number one, and I think if I had to choose another one, it would be number three.

DR. GARZA: All right.

Dr. Baker?

DR. BAKER: I think the real question here is what should the recommendation be? What's really necessary? And so, the question really is should we include references at all, and I believe that we should.

I think it should be a recommendation that references be included, and I think I would go with number one that all three references ought to be included, because I don't see how you can decide among the others which one you want to do.

DR. GARZA: Dr. Briley?

DR. BRILEY: One. I'm like Ginny. One. But if I had to go for another one, I would go for three.

DR. GARZA: Okay.

DR. THUREEN: I am presuming that, with on-line references, that it would be easy to get the three references standardized, accessible, and relatively easy to compare data to those, and once you set up the databases, that in the future it will be very easy to do,

and once you get to that point, I don't see why you wouldn't do one.

The pertinent information for the formula company is primarily the two formula comparisons, but the information that could be gained for all of us really comes under number one, especially if it's not an excessive burden.

So, I would say number one, and a distant second would be number three.

DR. GARZA: Dr. Denne?

DR. DENNE: One and two, with a preference to one.

DR. GARZA: Okay.

MR. KUZMINSKI: Three.

DR. GARZA: Three and three?

MR. KUZMINSKI: Three and three.

DR. GARZA: All right.

Well, with two exceptions, everyone selected number three. With a few more exceptions, one was the next, as I read it, and then two and four were less.

Now, with one and three --

DR. BAKER: I don't think you counted right.

DR. GARZA: Well, three was, except for Denne and for Dr. Downer, on everybody's list, I think. Number one was not as general, but it was on most people's list but not on everyone's list, fewer than number three.

So, let's go to number one and three, because they seem to be the most popular, and I'll take a show of hands between one and three. You have to select between those two.

So, those that have a preference to one, would you raise your hands?

[Show of hands.]

DR. GARZA: Okay. So, we have everybody but two.

And those that would select number three.

[Show of hands.]

DR. GARZA: Since number one includes three--how is that for confusion?--then I think that we're somewhat consistent in our advice to the agency.

Most people prefer number one. Everyone sees the breast-fed group as a necessary reference. There are two individuals who thought that perhaps was not necessary but they could live with that.

All right. Well, now, having done this, I think we've done B, but let me make sure that you agree with me. We talked about merits and values and ranked. All right.

Now we are down to number 7. We could either begin this discussion or we could--I don't know whether sandwiches are out there.

You could go now, take 15 minutes, bring your sandwiches is, and we could then work through lunch and get through number 7 rather than trying to break it up.

So, do you want to do that? Take 15 minutes. Let's get back here at 11:45. Bring your sandwiches with you, and we will try to get through question 7, and what I'm going to do with question 7 is to ask for a volunteer using a specific example of what would trigger a growth study and, on the basis of that concrete example, to suggest guidelines or criteria that led you to identifying that as an example.

Then I'll go down the committee, asking several of you for your examples and criteria and guidelines for coming to that example, with the hope that soon we will hear echoes of the reasons that led you to that, and if we hear echoes, then we should be able to get through that discussion fairly quickly, because we would have done A, which I think is the--what we're going to be able to do.

I don't think we're going to be able to identify all of the specific changes, obviously, that would lead to that, but we can generalize or come up with criteria or guidelines and give examples of how those criteria and guidelines, if we use the strategy that I'm suggesting. Is that acceptable to the group?

Dr. Stallings?

DR. STALLINGS: Thank you. I just wanted to make a couple of comments that came up during break and to be sure that they're part of our general discussion, as well, or knowledge.

In talking with Roger, it appears that the industry data on breast-feeding babies, which is extensive, might be able to be available, you know, in a form that we could all do.

Also, in talking with Dr. Fomon, only about a third of the data on the breast-fed infants there have ever been published for them, so there might be an opportunity to mine the Iowa longitudinal data set more specifically, particularly between the birth and four-month window that we're looking at.

So, I just wanted to mention those, that there may be better information for us in the future, and it represents great cooperation.

DR. GARZA: All right. Very good. All right, then. Let's get back at about 10 till.

[Recess.]

DR. GARZA: I want to thank the committee for being so compliant in having such a quick lunch.

So, we're on to the home stretch on question number 7.

We've got about two-and-a-half hours to get through it. So, I do think that we ought to be able to through it.

Of course, I may have nixed it in the expression of optimism. I hope not.

I asked the group to think about this, because I thought it would be much more efficient if you had had a chance to reflect last night on guidelines and criteria that one can use to determine the need for a clinical study intended to provide assurance of normal physical growth if one took an example of what, in your minds, would trigger such a study, and then, with that concrete example, illustrate for the group what general principles or criteria you used in identifying that specific example.

Let me ask for a volunteer. Who would like to go first?

You notice that I didn't choose anyone, because I want to keep my friends.

There's this great adage in food and nutrition that friends come and go, enemies you accumulate.

No one, huh?

Dr. Stallings, thank you for rescuing me.

DR. STALLINGS: Okay. So, I'll--I'm sure I don't have all the details that Bert's really going to want, but this will at least start the discussion.

So, my proposal was to study term infants, and my question was, on an infant--the term infant formula that has the soy protein--and one of the examples on the table was that there is the potential process for stripping the isoflavones out of that, so that you would be taking something that we have experience with, which is soy-based feeding--that you would be making a major manufacturing change.

So, in theory, I said it was from the same source, assuming that the stripping and all of that would be done by the company but that there be an assumption that it may actually have to go to a different source.

DR. GARZA: This wasn't soy that was grown in a corn field.

DR. STALLINGS: Right. And I was assuming that I would start with the idea that the same amount of protein content--so, the grams per kilo for baby, a normal feeding--I didn't have any intent to change that.

So, the inclusion criteria would be term, and I think that's been described as greater than 37 weeks, or I usually use the 38 to 42.

I stumbled even on the exclusion criteria trying to think about what we've all been working on, which is test the new product in the population that it will serve, and soy basically has a number of uses.

You know, one is cow milk protein that sometimes is used, although there are alternative products, lactose intolerant, and then in real clinical practice, it's often just used as the formula you try when the baby, quote, has "feeding intolerance," so it's not really coming with a real diagnosis.

So, I decided not to exclude anything. It was the decision.

And then trying to get into a protocol--I think this kind of a chain certainly merits a feeding study, as well as all the pre-clinical work that would have been done.

So, again, this was before much of the discussion today.

If I had a wish list, then I would have had, in essence, a four-armed study. So, we may have modified that already but that you would have a breast-feeding group as sort of a standard, you would have your regular soy formula, you would have my new modified soy formula with decreased isoflavones, and I was wondering about the strength of the data, and it probably could be provided historically, but again, to look at the growth of children on cow milk protein versus soy milk protein, just to benchmark that difference, as well.

So, then I was trying to think about where would I do the study, and as we all know and have talked about,

you can't exactly randomize children to breast-feeding. That has to be a family choice, and formula feeding is a family choice.

But then could we have a study where we would have families' consent to be in a study where they were randomized to regular soy protein, a new soy protein, or regular cow milk product, whatever the comparable product would be.

Then I had the idea that the birth weight would probably be historical, because we're not enrolling while they're in the nursery and the stay is so short, and then use the time-line--and I want them enrolled at least by 14 days, preferably by eight but certainly by 14, agreed with the work we did yesterday on weight and length and height and at the study assessments through six months, and I was actually wishing that I could have a 12-month data point for growth.

And then when I looked at, here, growth being your primary outcome, trying to follow that, there would be a number of other secondary outcomes if we were to take this approach, and those would be really, I think, two things.

One, part of the interest in isoflavone-reduced products is that is there any indication of estrogen effects on babies during this time? So, there could be physical examination and potential bio-markers, blood

tests that would follow that, and those might be done at one, three, six, and 12 months, not at every assessment, and probably the three-month is the highest dose exposure of the formula, because it's before most complementary feeding has started.

So, you know, the one-month, probably the exposure is highest because of volume, but I thought those were important.

And then the pre-clinical and the scientific review would have given--and the review of the actual manufacturing would have led to, are there any, for example, vitamin and mineral blood tests that need to--are we putting anything at risk by the time we've gone to this new manufacturing or new source, so that there might be some other biochemical assessments that would need to be done.

So, I came out of it with that kind of a study where growth is still the primary outcome, but there would be two types, potentially, of secondary assessment that I would be interested in.

One is the estrogen, and I guess the issue there is I know that it could never be powered to pick those up, because if they exist at all they're rare, and the vitamin and mineral data could probably be powered reasonably well, I would think, if there were indications from the manufacturing.

So, that's an overview of things to --

DR. GARZA: Okay.

As I listened to the design of the study that you were thinking about, were the criteria and principles that led you to that--because it was a substantially manufacturing change, I mean the idea that we're stripping something, that one was dealing with a potential special vulnerable population in that these kids, if they're generally put on soy formula, it's a second formula.

It's not generally a primary formula that's used, but either because they were intolerant or developed lactase deficiency or whatever, but they were an especially vulnerable population, and that there may be the involvement of bio-active factors that could influence growth.

Are those the sorts of criteria that led you to say, well, this is what would trigger a growth study, and are there others that one could generalize, so that as we look at the example that you gave, and others, one would be able to provide some guidance to say, well, if the change involves any of these factors, then you probably ought to think very carefully about the need for a clinical study or, conversely, one that look at growth.

If it doesn't meet these, don't worry about it.

DR. STALLINGS: I think you captured what I thought of also as my general principles. The only thing I realized as I was getting into this is, with such a major manufacturing change, you have to do the growth study.

If this were to stay a marketable product, I could see there would be a time in the foreseeable future where there might be questions that wouldn't require a whole growth study but might be going back and doing biochemical studies, that kind of thing, as we learn more about it, or again, you know, maybe there are vitamins, their bio-availability, things that change and things like that.

But yes, I think you got the major principles.

DR. GARZA: As I compare those with Dr. Bier's guidelines for when one would need a clinical study, the one--I mean and he mentioned others that obviously--that I have not from that example.

The one that didn't seem to be covered in his white paper was the involvement of a potentially especially vulnerable population, I mean that if you're dealing with a population such as the one that you might expect to be on soy, then you probably ought to have a higher bar.

DR. STALLINGS: As a clinician, also, I think the especially vulnerable population might be the

children with very short gut and the even more specialized products.

I think in today's environment that the soy product is so--used in so many different indications, many of them are probably not truly especially vulnerable.

We use it in that group, but I wouldn't want to say that I only want to go to children who, you know, had known, for example, protein or lactose, because it such a commonly used--so, I was trying to use that idea, where is it really used in modern practice, and this, I think, is generally used in many otherwise--well, in many healthy children, not otherwise healthy children, as well as having a special place with some specific GI or allergy diagnoses.

DR. GARZA: Do we have another example to help us work through identifying criteria or guidelines that would trigger a clinical study?

Dr. Heubi?

DR. HEUBI: I have an example, but it's pretty esoteric. But it's fairly relevant.

And that is my suggestion was a infant formula company would decide that it was appropriate to include epidermal growth factor in their formula for inclusion in a pre-term infant formula because there may be evidence that EGF reduces the risk of necrotizing enterocolitis,

and so, as a consequence, that addition, since it's really not been tested in humans, ever, as far as I know, in terms of as an enteric administration, would require a clinical trial, partly because you don't know about safety, but also you don't know about whether it would affect growth.

It may actually have an enhancing quality for growth that we currently don't know.

So, you would select a population of pre-term infants that would be probably 1,500 to 2,500 grams, the group of individuals who would be at risk, or even smaller, for NEC, and it would require a large population of patients to study to define whether there was really a clinically significant reduction in the rate of NEC within that population.

It would obviously require a comparison to a comparative formula that would be without epidermal growth factor, and your end points would be not only measurements of growth but also incidence of NEC, and as John presented yesterday, it would require a large sample size to be able to answer this question. It's a specific health claim, yes.

DR. GARZA: So, what one would be--you're dealing with a factor that's not been tested in humans before in terms of in a food in an especially vulnerable

population that might involve growth. That's one, in addition to the other three we talked about.

Another which I thought was interesting, when you said, well, here's a factor that's in human milk, and Dr. Bier has said, look, the fact that it is in human milk doesn't necessarily preclude a growth factor or a growth study.

Would you entertain the opposite one, to say, well, given the fact that any substance, bio-active factor that we don't have experience with, other than in human milk, should trigger one, because these are bio-active factors that act in concert with others, and we're not quite sure they might act, in isolation of everything else.

Epidermal growth factor is part of human milk, but so are a number of other growth factors. If you just provide in isolation, what is the outcome?

DR. HEUBI: That's a relevant question, too.

It actually sort of begs the issue of would you try to concoct a mixture of these to include in infant formula and do a study of that nature, but we're not designing their study for them.

DR. GARZA: But you're saying that anything that--a bio-active factor, whether there is experience--recognized to be part of human milk--is really irrelevant, I mean, that, in fact, you probably will need

a study, because we don't have an experience with that product in isolation.

DR. HEUBI: Yes, this is a circumstance in which a two-tail test for growth would be absolutely essential, because you don't know whether it might have a positive or a negative impact on growth.

DR. GARZA: So, not being tested in humans and its bio-active nature--that second one, I think Dr. Bier had in his paper, as well. Okay.

Dr. Clemens?

DR. CLEMENS: Thank you very much.

The hand-out you received yesterday, perhaps in the e-mail, as well, talks about the potential change that we might see in the infant formula now, and we have experience of what we have gone through, we might see in the future.

I think that was a very nice example, Jim, regarding EGF.

You see it as a flow diagram that focuses in the decision, how do you get down to the point where you decide to make a clinical trial, and that helps us focus on the question of item number 7.

Using Jim's example, you can see that perhaps we don't have sufficient hands-on information at this point in time, even though it included a breast-milk, addition

that requires a processing change under current food science and technology.

That would trigger, automatically, a clinical trial.

So, what I wanted to focus on is the fact that some of the issues we'll be discussing in the next two hours really go through this flow diagram decision tree matrix, and then you will look at the experience in a matrix, whether you're moving isoflavones from soy, what kind of data set are already available in human consumption as well as other studies, what processing changes, and maybe it's a processing change that would dictate initial clinical trials, in addition to physiological requirements.

So, look at nutritional adequacy as the bottom line, and if we think, in theory or through processing or through whatever change we have to go through, the ingredient or through the processing, that would dictate we'd expect a change in growth or impact on nutritional adequacy, clearly we would do a clinical study.

DR. GARZA: Dr. Anderson?

DR. ANDERSON: I wonder if I could follow up and ask Virginia some questions.

I'm way out of my content expertise here, so if I say something really stupid, you'll forgive me.

Suppose, prior to your study, there were two previous studies, one done by taking isoflavones--removing isoflavones in a dietary supplement which was directed towards the elderly and the clinical trials there were already completed and were found to do what you expect dietary supplements in the elderly to do and there were no impacts on adverse events.

And suppose, in addition, there was a study in children who, because of their medical condition, needed dietary supplements and that study had already been done, again with the same processing to remove the isoflavones, a appropriately conducted clinical trial showing that, in, let's say, eight-to-12-year-olds, the product without the isoflavones produced the same effect as the product with the isoflavones and there were no obvious adverse impacts.

How do you feel now about the necessity for a trial in infants?

DR. STALLINGS: Probably unchanged. The issues of exposure to the estrogen component is, I think, very different in the very young, growing child.

The per-kilo exposure even in the residual amounts or in the previous amounts would be quite different, usually, from the food sources.

So, I don't think either of those would be good models to test either the growth question, because of

the--in essence, the infant growth spurt that we've been talking about, nor optimal for testing the question of whether very low bio-active components are having a biological effect, and we know in newborns that changes in some hormonal--some enzymes--that with relatively low amounts of estrogen you can estrogenize boys and with relatively low amounts of testosterone you can testosteronize girls.

So, there are some things that are fairly unique in that setting, but it's a good question. But in those two examples, they don't meet the dose exposure, and neither of these populations would have the growth.

The per-kilo in health infants, the protein intake, you know, is probably two to three grams per kilo.

By the time you're a 12-year-old, it's probably about one gram per kilo, and elderly, honestly, we don't have as good a handle on, but in healthy adults, we tend to think of it being .8 grams per kilo.

So, even the protein sufficiency question, which is inherent to changing a protein source--probably those are not great models.

So, I would be looking for a younger, rapidly-growing group.

DR. GARZA: So, would we then modify one of the criteria that Jim introduced to indicate that, in fact,

it's not enough that it hasn't been tested in humans but that it hasn't been tested in children, so that the default ought to be, gee, do you have information that is developmentally specific, dose specific, because of autogeny of development, etcetera.

Okay. That was very helpful. Thank you.

DR. SIGMAN-GRANT: But didn't we say that what we'd require would be that the formula would be tested for the population for which it was intended?

DR. GARZA: In terms of triggering that, if you had epidermal--let's assume that we had epidermal growth factor data in humans that had been safe in the elderly or in an adult population. The fact that you didn't have it in children would still trigger or be one of the factors that at least the FDA would use in determining whether or not they would recommend or industry would decide to do a clinical growth study.

Dr. Anderson?

DR. ANDERSON: The reason for asking the questions is that I think that there's probably some continuum, and the particular example here is probably not the right one, but I can sort of imagine that there might be another instance of a major processing change in which there was information from other sources to suggest that the preponderance of that evidence would suggest that the change would have no adverse impact either on

growth or adverse effects, and so, I think we need to, you know, test that boundary as we may have these discussions.

DR. GARZA: Knowing full well that this has been a topic of recent enormous concern nationally in terms of when you require testing in children, I don't think we'll come to resolution on that one, and we probably shouldn't try at this meeting.

Okay. Any other examples that will help us go through this development of guidelines and general principles?

Dr. Denne?

DR. DENNE: Not so much an example but perhaps a comment on the previous AAP guidelines about what might not trigger a growth study, and I mean, for example, fairly wide ranges in changes in energy concentration and very wide ranges in protein concentration by the AAP in 1988 suggested that those didn't require growth studies.

I would think that, at present that wouldn't be acceptable. I mean a change somewhere between two and four-and-a-half grams per hundred kilo-calories, according to the AAP, wouldn't require a change.

It would seem that, under our revision, that might be different, that major changes in macro-nutrient content would require a growth study.

DR. GARZA: This brings to mind the suggestion that was made, I think again by Dr. Bier, that we ought to take a look at the LSRO, DRI, and other processes to see have those ranges been narrowed by any of that information, because those requirements have been looked at, and I think you're right that we ought to probably go back and get more quantitative, then we will have an opportunity to do that here, and those may be guidelines that we can use to help determine what would be appropriate.

Dr. Thureen?

DR. THUREEN: Yes. I'd like to know if there's any plan to adopt the LSRO recommendations by the FDA?

DR. TAYLOR: In order to provide for the final set on nutrient recommendations, we, of course, go through notice and comment rule-making, and all available data, including that from LSRO, would be part of the consideration. So, it will certainly be considered.

DR. GARZA: All right.

Any other examples?

DR. SIGMAN-GRANT: I had an example of adding cholesterol to bovine iron-fortified commercial formula.

There are some studies in baboons that suggest--there's some previous animal studies that suggest that it, again, is a compound found in human milk.

I looked through Dr. Bier's criteria, and it will fit under almost any one he listed, but I think that would be an example where a growth study would be required, particularly since it's such a controversial sort of ingredient.

DR. GARZA: Did you find any of the general principles or criteria that Dr. Bier discussed in his white paper inappropriate in terms of triggering the study?

That doesn't mean that it would necessarily be exhaustive but that, as you went through the cholesterol example in your mind, did they all pretty --

DR. SIGMAN-GRANT: Yeah.

DR. GARZA: --fit in your mind that that should be looked at?

DR. SIGMAN-GRANT: Almost every one of them. I think addition of an entirely new compound, it's a formula change. Well, we don't have nutrient levels established. So, that one wouldn't apply to this.

But compound known to affect hormones, growth factors--I think most of them, except for the one where it hasn't previously been established.

DR. GARZA: As I go through the list in my mind--and I may not be remembering them all--the only two--and one could construe, perhaps, that some of them would be inclusive in the list that he provided in that paper--is

the extra care if the formula is directed at an especially vulnerable population and that, in fact, one ought to look very carefully at those changes.

Premature might fall into that group, not only the type of infants that Ginanne's example gave us, and the addition of a new factor, but I guess that would be in there, as well, I mean exactly.

So, that may be the only one.

Dr. Heubi and then Dr. Anderson?

DR. HEUBI: My only comment about cholesterol is it actually is present in infant formula in varying concentrations, and the reason, actually, it would fulfill criteria probably would be it would require a new formulation to do this, correct?

DR. GARZA: Dr. Anderson?

DR. ANDERSON: So, perhaps I could ask Roger to comment, because the criterion 4 was that a study was required when an entirely new compound was added to infant formula, and yet the decision tree chart seems to suggest that if the additional ingredient was determined to be generally recognized as safe for infant formula, its addition was supported by well-accepted scientific rationale and/or experience in the manufacturer's formulation, I assume other formulations, and raised no reasonable expectations of a significant adverse impact, that no clinical trial was required.

DR. GARZA: Before he answers, is there a separate GRAS list for infant formula? No, there is no special GRAS list for infant formula. So, it's just--you're suggesting that any GRAS substance --

DR. ANDERSON: No. I'm suggesting that's what the decision --

DR. GARZA: I don't think any of us would agree with that, but let me ask Dr. Clemens. I mean Dr. Benton gave us examples where that could be a problem in young infants.

DR. CLEMENS: Even though it's GRAS, it may not be appropriate to put in infant formula, is the bottom line, and we have to assess the science behind putting a particular ingredient in infant formula.

If you want to use the cholesterol issue--and thank you, Jim, for making the comment that all milk-based formulas do, in fact, contain cholesterol at some levels, but also the emerging science would suggest--if you want to use that as an example--suggest there is points of addition you want to consider, what happens to instability, and a new matrix is not associated with reliable proteins, is not associated with microns.

So, how is that metabolized? How does it impact cholesterol biosynthesis or degradation? All those things need to be considered, and clearly, it's likely that we would do not only a growth study, Madeleine, but

also do a lot of metabolic studies to justify that position before presenting it to the FDA.

DR. SIGMAN-GRANT: It was just an example.

DR. GARZA: I do think that it's helpful to go back to criteria 4.

DR. HEUBI: It was a good example, and actually, it was a good example for maybe the wrong reason, because it actually would require reformulation, not because it's a new addition.

DR. GARZA: If we go to criteria 4, though, the example that Dr. Anderson just gave us about GRAS substances, criteria 4, as suggested in Dr. Bier's paper, doesn't make a distinction between GRAS and non-GRAS substances, just as if it's a new compound in infant formula.

DR. THUREEN: Dr. Garza?

DR. GARZA: Yes?

DR. THUREEN: Maybe I could comment. And this is an example from the decision tree paper. They said here are examples of substances that may not necessarily require a clinical trial, and it said "addition of minor constituents added for potential nutrient contribution but for which there is no reasonable basis to predict that they would materially impact nutritional adequacy," and the example was L-carnitine.

I thought that was a curious example and that that's sort of a new ingredient that I think has been put in great question, and the implication here was that you didn't necessarily need to study it, because it's well enough understood.

DR. GARZA: I think the decision tree is very useful for your background, but it's not something that is on the table as something we're going to adopt.

DR. THUREEN: Right.

DR. GARZA: If we start doing that, then we have to go--also, there's been another decision tree that was suggested to us by Dr.--or Ms. Heiser to treat it as a drug, and I don't want to go down that path.

DR. THUREEN: I didn't mean to talk about the decision tree specifically. It's just that this is a new product that I think would, by definition --

DR. GARZA: It's an example like the cholesterol one.

DR. THUREEN: Another example.

DR. BAKER: I'm sort of--I'm going to give another example, and I'm a little bit afraid of what's going to happen with this, but looking at the decision tree again, to me, it does seem like the decision tree does reflect some thinking about what are in the regulations.

So, I think the decision tree is worth looking at.

I do note, however, if you get down into the bottom of these, it always comes to a study is unlikely or likely.

You still have to make that decision, and actually, we're working below the decision tree. We're trying to decide how to decide this last thing in the decision tree.

DR. GARZA: Well, to the degree, Dr. Baker, that you can take--extract either general principles or criteria that you think the group ought to be considering from either that tree or anything else we've heard, that's fine, but it's not the tree we're looking at.

DR. BAKER: We are actually looking at the bottom box of this decision tree, so that what goes before that is not really relevant. Well, it's relevant, but it's not what we're considering at this time, and the reason I'm bringing the example up that I am going to is that, if you follow the decision tree and what the industry has given us, you probably wouldn't have to do a growth study in this case, but I think you clearly would if you follow my logic here.

The example--I don't want to embarrass the FDA, but the example is boiling water to powdered formula for pre-term infants, and this was suggested because--it was

to eliminate contamination in powdered formula, and the industry has said, if they have a recommendation from an expert body, that they would accept--would make that change without a study.

But it's very clear that boiling water to powdered formula changes all sorts of things in a formula, and it would definitely--if you were going to actually go through with that--fortunately, we have backed off that a little bit and we're not going to go through with it, but if you were, it would definitely require a growth study.

DR. GARZA: So, that would be based on the general principle that if you're going to change the composition--so, if you're going to be changing the nutritional composition of the formula--I think that's, again, one of the criteria in Dr. Bier's paper.

Dr. Downer?

DR. DOWNER: In doing my assignment last night, I looked at iron, and we know that most of the formula in the United States do use ferrous sulfate, and I wanted to see, if we were to use a different form of iron, it might have been interesting to look at, in general principle, what some other criteria would be to address this.

Again, this is not factual, just hypothetical. That's what we're going from. And so, in general, I think that would trigger, I think--and essentially what

would trigger the growth study would be if there were any--looking at bio-availability.

That would be something that I'd like to look at.

Also, the impact of this new iron source on the other nutrients that would be available. So, how would it impact?

Also to look and see if this new product, whatever this new iron source is, how would it perform at least with the old product and also against breast milk formula?

I'd also look for metabolic, physiological, and endocrinologic changes in the new formula, and also look to see how this new iron formula would impact on growth, particularly the growth parameters that we set forth, and of course, taste would be something I would look at, acceptability for the infant.

So, those are some of the things that I noted here.

DR. GARZA: So, that would still fall under the new formulation. If you're going to reformulate it, then for all those reasons, you would want to --

DR. DOWNER: Yes.

DR. GARZA: Okay.

DR. GARZA: Dr. Kuzminski.

MR. KUZMINSKI: Thank you.

We did not collaborate, but I chose exactly the same example.

But I think--and I was being a little bit more specific, but some of the industry may consider a frivolous recommendation of changing not just the source but source and type, ferrous sulfate to an encapsulated reduced iron, where the new technology may provide stability to the reduced iron, and so, we're assessing the effect of the efficacy of the encapsulation and then also the impact upon the other nutritional components of the formulation.

If this is new technology and is driven by supplier problems with the traditional source of iron, ferrous sulfate, then a criteria also may be the existence or non-existence of internal experience with the new component, whereby this particular example may, in itself, not drive the need for a growth study but may have an effect on other components within the formulation, chemically, organoleptically, for acceptance that may drive the need for a confirmatory study, if you will, a growth study.

DR. GARZA: So, again, it would be a new formulation, in essence.

MR. KUZMINSKI: New compound.

DR. GARZA: I am not hearing marked deviations from at least the background material that we got both

from the agency or from Dr. Bier or necessarily the general principles that are outlined in anything we've heard in any of the presentations.

Is that because it's too complex an issue that we can deal with or because everybody's exhausted, that you gave it enough thought?

How about some of you that have not given us your examples?

DR. THUREEN: I have an example of a pre-term study, which we haven't addressed, and my example was a new fat gland with possible enhanced growth, fatty acid profiles more like infants fed breast milk, possible lower cholesterol levels in infancy and possible positive effects in neuro-development outcome.

This product has been studied in term infants and shown essentially no effect in growth, but there was a slight tendency towards long-term neuro-developmental positive benefit, and those studies had only gone out to 18 months, and now this was to be studied in pre-term infants, though there had been recent reports of increased diarrhea in term infants.

So, the objectives were to study this in this new pre-term infant population, and what would make it different is that it would be a new population, essentially that had not been studied before, a vulnerable population.

We'd want to study effects in neuro-development outcome and look at effects on growth, and this would not only definitely require a growth study but may require a more detailed study done, both fat digestion and level of fat digestion, so we may need nutrient balance studies, and maybe micro-nutrient studies in case there was increased fat mal-absorption.

You'd have to look at absorption of other studies.

So, this is in the category of effects on absorption of other nutrients.

DR. GARZA: But also, I mean there would be a formula that is now going to be intended for a brand new population that's never been tested. So, in essence, it's a brand new formulation.

DR. THUREEN: And new formulation.

DR. GARZA: And that would go ahead and trigger, than, a study, because it would be intended now for a population whom it had never been evaluated, and I think that's not a guideline or a criterion that is in Dr. Bier's paper. I think it is part of--maybe not--of the other background material we got from FDA.

Dr. Clemens?

DR. CLEMENS: Actually, I appreciate the comment on iron. I did research on iron over 20 years ago, so that's pretty close to my heart. Actually, ferrous

sulfate is a good example, and we've used it in infant formula for a lot of years, and if there's a change, emerging technology, yes, all the studies that have been suggested--metabolic studies, balances studies--those kinds of things are already addressed in the academy guidelines.

In addition to the fatty acid issue that you addressed in pre-term, those, too, are addressed in the academy guidelines.

You change the fat source, change the growth profiles that are significant based on the scientific evidence, we actually do the digestibility issues, we address the balance issues, we look at stools, we look at a lot of different things, as you can imagine.

So, both kinds of guidelines were in place, and based on scientific background, the knowledge and experience again, we actually won't trigger clinical trials, because it's your point, it makes good sense.

DR. GARZA: Dr. Sigman-Grant?

DR. SIGMAN-GRANT: What about an ingredient that's, say, genetically engineered or produced through a different technique? Would that be something that might require a different criterion, if it's the same ingredient but production is different?

DR. CLEMENS: That's a fair question. I can give you two examples.

We look at canola oil, based in Canada. It's a low-erucic acid, a seed oil, and we've agreed in this country not to use it.

Matter of fact, a number of organizations across the world have agreed not to use it because of the presence of erucic acid, and we certainly concur with that in the pediatric population, even though Codex, I think, agreed that it could be used.

WHO, however, has not agreed that it should be used in infant formula.

In terms of protein, let's say, biotechnology, all the soy protein used in this country in infant formula is, in fact, Monsanto-derived, and it is through years of usage and growth studies, it's been deemed to be nutritionally adequate.

Now, if there's a new ingredient that's on the table, in fact, we would study it just as rigorously as anything else.

DR. GARZA: Would that trigger a study because it was a new source? What that considered a new source of soy and, therefore, a new formulation and, therefore, was re-studied when they made the transition from traditionally bred to genetically modified soy?

DR. TAYLOR: The answer to your question is a very difficult one, because you know, we're standing on the precipice of what does that mean, and remember, it's

GRAS for intended use. So, there's GRAS for whatever the end point is, and I'm deliberately not going to answer your question, because I don't think we have a history of knowing how to answer your question.

DR. GARZA: All right. The only reason I was curious is because we have one guideline that says, if you have a new source--so, if the new source is a new source --

DR. TAYLOR: What is it? You know, we're back to that problem. Is it a new source? If it is a new source, it's down on path. If it's not a new source, it's down the other.

So, new source, yes, but what's a new source.

DR. GARZA: It's a good point, because in fact, one looks at the criteria that says new source, and it's a definition of not what is is but what is new and whether, in fact, one would find, if the source has been modified in any way, whether that qualifies as new.

Dr. Briley.

DR. BRILEY: I just wanted to ask who identifies whether it's a new source or not? Does the industry? Who does the identification?

DR. GARZA: Who has the regulatory responsibility to identify if somebody switches from one source to another?

DR. TAYLOR: This is a notification process, so the manufacturer comes in with a package. We have the right to object or not object.

So, they could assert it's a new source or assert it isn't a new source, and then it comes under our review.

So, it starts with them, and then we, of course, review the package.

DR. GARZA: For example, let's assume that BT corn, tomorrow, would become a significant source of some unsaturated fatty acids.

It would be the responsibility of the manufacturer to notify FDA that, in fact, the source of the fatty acids had now changed from a conventional corn to BT corn, or would you be required to identify the change by your own monitoring techniques, so it would be the manufacturer that--so, it's their judgement as to whether it's new or not.

DR. TAYLOR: We're talking about 412, which is the finished product. I want to distinguish between the 409 review, which is the actual individual ingredient and its coming in for GRAS, which is a preliminary process, separate from the 412, which is once everything--the individual ingredients are deemed safe, once you put it together, it works.

Now, that whole notion of working is where new source comes in. So, it's a very complicated world, but no, we don't have a monitoring to see what the industry is using for these formulations, if that's your question.

DR. GARZA: Does that help clarify it? Thank you. Because that's very helpful.

Dr. Anderson?

DR. ANDERSON: I'd ask Dr. Thureen to consider the reverse of the trial that she suggested.

Suppose that the previous study was done in well preemies and they were studied through to six months after expected delivery and that it all turned out exactly the way one wanted it to, and now the interest is in marketing this to term infants.

Do we need a clinical study?

DR. THUREEN: I think it would require a clinical study, because I think you have to assess growth.

It's a new formulation in a different population, physiologically different population. I think it would need study.

DR. GARZA: Would anyone disagree with that?

So that, as a general principle, anytime you move to a population other than the originally intended one, that the default ought to be a new study.

Obviously, people can submit information as to why that may not be appropriate, but that ought to be a trigger in considering the need for one, as a general principle.

Can you think of circumstances where that general principle would not--wouldn't even come into play?

Dr. Stallings?

DR. STALLINGS: It's hard to think of one that we could do theoretically, and I think we've got to remember that, if we use the population that you intend to treat, the pre-term infant formula will be fed to babies who are still in intensive-care units and are generally very sick.

Now, they're not so sick that they're not getting enteral formula, which is a point in the spectrum, but they're also capable of getting sepsis or any number of other things during that grower and gainer phase.

So, I think it is a very different time, and anything designed for that and shown safe there actually might have--might theoretically have a different effect in truly term babies without all of the stresses of being premature and in intensive care units.

So, I would have--I'm sure if we sat and thought, we could think of something, but as I go through

it, I mean, you know, energy, electrolytes, all of those--osmolality--all of those things are very different from the very young, critically ill--the small, critically ill baby to the term baby.

So, I would be hard pressed to do it.

DR. GARZA: Okay.

Dr. Anderson?

DR. ANDERSON: I can't imagine why one would do this, but suppose that the study of a new infant formulation was tested exclusively in full-term, low-birth-weight children, because there was an available source.

Would that be sufficient for marketing to normal term infants?

I'm trying to stretch the boundaries here.

DR. MOYER-MILEUR: My response would be no, because you're again looking at a special population that, in utero, has suffered some type of nutrient deprivation, even though they're born at term, and so, then to apply that may work in that population may essentially overfeed or over-nourish a healthy population.

So, I still think you're working with a different population.

DR. GARZA: We have a number of presenters, and I'd like to ask whether, in fact--those of you that

represented yesterday--are there other criteria or guidelines that, in fact, you haven't heard raised that you think the group ought to consider in going through this discussion?

[No response.]

DR. GARZA: Okay. All right. Well, I don't know whether we're going to--maybe we're done.

I don't know whether we're going to get anymore from the group, other than if we look at the guidelines, the criteria that are here, the discussion that we've had, I am not sensing that, in fact, we see that this is a deficient list in other than the few ways that we've talked about, and that is, if you have a potentially vulnerable population, that probably that ought to be thought through more carefully.

Everything else seems to pretty much under one of the existing guidelines or criteria.

The only other issue that's come up is that, under criteria four, that, in fact, that is a new--in Dr. Bier's paper--that that is under any entirely new compound.

Whether it's GRAS or not is seen as irrelevant, that if it's new, then there ought to be scientific data or something to back it up, but it ought to, by default, be considering as triggering a growth study, assuming that you had appropriate animal studies and everything

else that showed that it was going to be safe in this population, obviously.

All right. Well, then you've accomplished what I thought was impossible, which is very nice, and that is to get through this meeting early. I didn't think we were going to be doing that. I thought we'd be here till 3:00 o'clock and that this would elicit a lot more debate.

I thought we were going to be there with the genetically modified discussion that Dr. Sigman-Grant opened up, and I think that that would still fall under the criteria that we now have.

DR. HEUBI: So would pre-biotics, too. So, it's actually--it all falls under that category.

DR. GARZA: That's right.

DR. STALLINGS: Now that you're making us talk about it some more, just in the sense of clarification, as I understand it, though, it still would be based on industry deciding that changing from traditional to genetically modified sources constituted a new source versus this soybean or this soybean, that sort of thing.

So, maybe what--I can go back to Roger and say, does industry consider those kinds of--I mean particularly--I mean what we might have said 10 years ago when we first started thinking about this versus where

the public interest and elements of trust and all those other things are.

So, does industry--would that merit calling the FDA and saying we've just changed growers or our growers changed seeds for the soybeans?

DR. CLEMENS: We may not go back to the growers and say that our growers have changed seeds, but we do work--the industry does work very closely with the various suppliers of ingredients, and if they change their process, they change their technology, the industry knows about it, and they take it very seriously, if, in fact, they believe it will change the physical characteristics, as it was mentioned this morning, of that particular product, it will impact on nutrient bio-availability, if it impact on processing, ultimately will impact on growth, and if, under all those criteria, if we feel that it could impact negatively in any of those aspects, we will, in fact, do additional study, if warranted.

So, they are very, very sensitive to the change of ingredients, anything that the suppliers will do. Be assured with that.

DR. STALLINGS: Just to follow up--but the truth is, many of us think that changing the soybean source wouldn't do any of those things, but yet, we've not had a lot of experience in that.

So, the issue of--it's assumed to--you know, how are we going to make those decisions as some of the new agricultural products come down the line?

I mean it really isn't like traditional genetic engineering--breeding practices, the old thing, we're going to make a better soybean--hybridization, thank you.

So, it still is an issue of a value judgement or somebody going, you know, even though this is the commonly used source now, does it have any human impact, you know, and maybe the infants will be the canary, you know, in the cave, because they are the--probably among our most vulnerable and certainly the most rapidly growing.

So, you know, you guys have a lot of responsibility in this setting, because if you don't bring it up, the FDA doesn't have the authority to come and ask you those questions, the way the relationship stands.

DR. GARZA: Well, let's not get into this discussion, because we won't solve it, and it's part of 409, as we were told, rather than 412, and for those of you that were listening yesterday, that means that we're dealing with 412 and not 409.

I mean it is a serious issue, but it does come under another section, and one has to look at issues that

go way beyond what we have time for in terms of isoflavone content.

I mean there are lots of things that you would want to think about in changing from one formulation to another and potentially bio-active products being involved.

So, with that, let me thank everyone, unless there are other issues that are outstanding that relate to section 412 that we need to cover before we break up.

Dr. Baker?

DR. BAKER: I just have one last--does this mean that we're leaving the AAP 1988 guidelines intact?

DR. GARZA: We have not been asked to comment on the criteria. We've gone through the seven questions.

I think we've provided the answers that we were asked to give, whether it's three grams or two grams or one gram.

We can certainly be asked to come back and deal with that issue, but I think if we do that, then we need to look at functional outcomes much more carefully.

We've had some statistical presentations as to why two may be better than three and why even less than two--I think it was Dr. Grummer-Strawn's paper that said .2 standard deviations would get us to an even smaller--then there's the whole issue of non-linear versus linear, does it mean anything to say .3 over the first four

months or three grams a day when you know you've got a very non-linear--I mean, so--okay.

Dr. Taylor.

DR. TAYLOR: I'm going to do a formal thank you, if you're ready for a formal thank you.

DR. GARZA: Thank you.

DR. TAYLOR: On behalf of the agency, we do want to thank this task force very much for their involvement and input and, of course, all of the great speakers that we had today.

So, we're very pleased. You've provided a lot of food for thought, and we look forward to future discussions.

So, thank you.

DR. GARZA: Dr. Anderson.

DR. ANDERSON: At least on behalf of myself, I'd like to say how very helpful the white papers were.

In fact, they were, I thought, extraordinarily well-done, and I think that anyone observing the discussions--our discussions this afternoon and today realize how extremely important they were to forming our own views about these issues.

DR. GARZA: That's very key, and I think one of the reasons we were able to get through this as efficiently as we did was because of both those white papers and the presentations. So, you know, thank you.

DR. BRILEY: I want to say, on behalf of myself and probably the rest of the group, how great you are as a leader, and we appreciate so much what you've done.

DR. GARZA: Thank you very much. That's very kind.

All right. Well, have a great trip home, and I suspect we'll be meeting again.

[Whereupon, at 12:57 p.m., the interview was concluded.]