adverse events speaks for itself. So if we want to deal with that, I think we have to be thoughtful about how to do it.

My biggest concern is to pick up big things during the course of the study and be able to use the GI intolerance kind of data that would not rise to a serious level in an effective way.

And I think post-marketing surveillance is a minor part of--it's there, but I think we shouldn't rely upon it to give us much information. The 800 numbers are generally useful for the anxious parent and for the companies to get a little feedback on how things are going.

DR. GARZA: All right. Any questions?

[No response.]

DR. GARZA: I saw several people use the term independent board. Can you amplify what independence would mean?

DR. STALLINGS: In this setting, it would be people who had the scientific background both in what we're talking about, pediatrics and particularly in neonatology, in statistics, but not

involved in the study. So they wouldn't have been involved in designing that particular study and if it's an academic, their home institution would not be involved in conducting the study. So that if 20 sites were needed to do the trial, the board would need to come from places that was not doing the trial.

So, again, there is some art in getting good people to sit on the panel. I don't think it's as much of a challenge in this field because we have lots of places where we can do good clinical research and lots of places without standing neonatologists. But that's what I would mean by an independent board.

Now, the agency could decide that the board would have a representative, if they thought, from industry, but the model is that as the investigator or the sponsor, we would not be at the table when safety discussions and infant data were reviewed.

DR. GARZA: So you are suggesting a safety monitoring board for all studies, so there would be

one group that would be monitoring all clinical studies that would be evaluating formulas, or would these be independent monitoring boards that would be located within each locality?

DR. STALLINGS: I'm not sure. I would propose that we could set up a monitoring board that would serve--because there are not that many studies going on at once and the expertise that you could create might be better served by one board that sits. I think then the issues of having independence or appropriate disclosure would be very important. But you would gain a lot of expertise by there being a sitting board and you would get some uniformity of response to industry and to the agency, rather than one board sees this as an event worthy of a lot of attention and the other board would not.

That's not really been done before, but I think in the current clinical research environment and with many of us wanting our studies to be independently monitored to be sure that everything's going well, that might be an

interesting innovation.

DR. GARZA: Would any of you that have spoken before want to amend your recommendation, because I don't think I've asked and several of you have used the term "independent."

DR. HEUBI: I certainly do, and I would recommend that if we as a group believe that an independent board would be appropriate, that it be a board that will oversee all sites, that it not be located at individual sites, because that's one of the issues that we deal with on IRBs now because we're only seeing part of the elephant, if you will. So you want to see data from all the sites to be able to make a decision that is thoughtful in terms of determining whether there are trends or problems that exist in any clinical trial, whether it be formula, drugs, or whatever.

And in addition, I would say that I would exclude members from industry and that it would be appointed independent of industry, and the reason I say that is for their benefit that it be done that way. That way, no one would ever dispute that

there was a conflict of interest in terms of the review of these kinds of studies.

DR. GARZA: Would anybody else want to amend or ask questions of clarification? Mr. Dwyer?

DR. DWYER: I just had a clarification. What is the current process in terms of, say, the studies that have been done in the last five years, the major studies done by the formula industry? Do they have such boards? Are they in place? I don't know.

DR. GARZA: I understand from what we've heard that there are some who do. Dr. Carlson, for example, indicated that she had. Others have not. It's been pretty much on an ad hoc basis. If that's how--

DR. DWYER: What about the ones that are multi-site, multi-site ones?

DR. GARZA: That holds for multi-site.

DR. STALLINGS: And most of this work, by its nature, is done at many sites, and often just a few subjects at each site because of the nature of

finding the participants.

DR. GARZA: Do you want to speak to this directly?

DR. CLEMENS: Relative to that point and when following the 1996 guidelines, which are currently not part of the FDA mandate, the clinical studies which we've been involved in for the last ten years have included some sort of in-house safety monitoring board, but it's not gone to outside evaluations.

DR. GARZA: It's not been an independent board, then?

DR. CLEMENS: That's correct, but we have been doing the safety monitoring and reported the AEs, yes.

DR. GARZA: Okay. Are there any other points of clarification that speak directly to this point or anyone else that wants to amend what they meant when they said an independent monitoring board that would be in disagreement with either Dr. Heubi or--and the major difference that I detected there was the presence of industry on such a board.

As a point of clarification--I'm sorry, Dr. Hotchkiss?

DR. HOTCHKISS: Joe Hotchkiss. I have served on such a board for GRAS substances, not for ingredients, but sometimes those boards are appointed by the industry but are independent of that industry, and an industry who appoints a board that's going to submit information to the agency does so at its own peril. In other words, if the agency does not accept the independence or the qualifications of the board that you have formed, then you're probably shot down immediately and you've wasted a lot of time and money.

So at least in my experience, most companies are, not because they're particularly altruistic but because they worry about the agency rejecting the qualification of their boards, are usually pretty good about the boards that they appoint. So I don't have a problem with--this also puts the financial and logistics burden on the affected industry, which I think is good, rather than putting it on FDA.

DR. GARZA: Let me interrupt you, because you'll get a chance to tell us your recommendation on that, but in terms of clarity, is there any information you want to give the board, Beth, or--

DR. YETLEY: No. I had a clarification question.

DR. GARZA: Okay.

DR. YETLEY: It seems to me--I understand the need for an independent review board during the course of the study and in terms of human subject protection and what not, but I'm not clear, then, how that impacts on the question of if an independent review board had not found adverse events to be treatment-related and then the data comes in with significant differences in adverse event numbers between the two groups, how then do you make the decision about the usability of the study in terms of supporting normal physical growth? Do you see what I'm trying to say? It seems to me like there's a two-step process here.

DR. STALLINGS: And I think you're right. The data safety and monitoring board really is

about safety of adverse events and, in essence, signing off on those data. Then it comes to you as an agency to review, and if there are differences, I think you still have the question of does that influence the acceptability of the data.

The primary outcome data that we've all been talking about is growth, and if the growth were not different, that currently being the benchmark, and the serious adverse events were not highlighted by your safety monitoring board and the non-serious ones were not also, I think you would have to move ahead with it was not deemed related to the study and move ahead with it.

DR. GARZA: All right.

DR. STALLINGS: I mean, that gets back to randomization work and was the study conducted by protocol, and assuming all of those qualifiers are met and that the board reviewed both the serious and non-serious adverse events and didn't act.

DR. GARZA: Let's move on, then, to question three. I think we're now commenting more on the recommendations than clarifying.

DR. STALLINGS: Question three is the issue of attrition rates, which was eloquently addressed by Dr. Anderson and I would concur, and I agree that I believe in the well-designed, probably randomized study, that if you have a big difference in dropout rates, it's incumbent upon us to know why, and that would be the first step. And then it still leaves the judgment step to the agency, but after you have all of that information to decide whether you think it invalidates the study. If the answers of why are not available, then I think there's a risk in accepting the data.

DR. GARZA: Okay. Dr. Giacoia?

DR. GIACOIA: I think we have been using two terms interchangeably, independent panel of experts and DSMB, and I think we may need, first of all, to look at what's happening on the other side of the agency in CDER, where they're coming up with proposed rules for DSMB on drugs. I think that the issue, some of it, the recommendations of just a priori consultation with the agency, it worked very well in CDER and I think you proposed that and I

think it's a very good idea and there, an independent panel of experts would be very helpful.

DR. GARZA: All right. If there are no other questions, we'll give Dr. Thureen the last word among the temporary members.

DR. THUREEN: Thank you. I assume that much of what I--I know that much of what I say now will be just a reiteration of what's been said before.

DR. GARZA: That's important, so don't worry about that.

DR. THUREEN: But when you think about that these recommendations have basically been redone every ten or 15 years and trying to project how our recommendations now should affect what happens in the next ten years, it's always difficult to know what's going to happen, but I would anticipate far more studies are going to be done now at developing formulas for high-risk populations, that that's a big area that we're heading into, so that it's incumbent on us to try and anticipate what will be done and to develop

recommendations that will support not only the infant and the best research that can be done, but really to help support an industry which has done a remarkable job to date.

So it disturbs me a bit in that at times it seems like some of our comments are adversarial towards the industry and I hope they don't take it that way at all. In our discussions privately, a lot of what we've said is we have to protect an industry that's done such a remarkable job, so I hope it's taken in that spirit.

DR. GARZA: Point of order. Our jobs as committee members here is to protect the public. The industry can protect itself. Our main goal is the public good, and I want to make sure that all of us recognize that even the industry representative, he is on this committee representing the public good, not representing this industry.

DR. THUREEN: Regarding question number one, points A, B, and C, categorically, theoretically, presumptively, my answer would be

no, but that there are exceptions. Again, it's a basis of physiological differences between preterm and term infants, between perhaps one product and another, and I think it's almost always going to be that any study done has to be redone in preterm infants that's been done in term infants.

Going the other way, I think it has to be considered on a case-by-case basis and that a repository of case examples and guidelines, such as the industry has already started to develop, would be very helpful to provide a framework for answering question and that it may not be one single--and I'd also recommend that a board be available to review studies before they're even instituted to help facilitate studies being done in a proper manner, and that it might not be one single board but a panel of experts that can be available for different types of studies that can be called upon that would be willing to make a long-term commitment to be on this to facilitate approval of different studies and study designs and make commentaries.

Again, I think that these should be reviewed before initiating any studies, and I think in many instances, depending upon what the study is, available data that might preclude having to redo studies in term infants if it's felt that there's adequate scientific justification and other data out there that would make it not reasonable to really have to redo this study, that that could be decided by an independent board.

DR. GARZA: Thank you. Any questions, points of clarification?

[No response.]

DR. GARZA: Thank you. Number two?

DR. THUREEN: In regards to question number two, I struggled with this because it seems like a two-part question that's not related, sort of like the question, is it farther to New York or by water?

[Laughter.]

DR. THUREEN: And when I look at this, I think that a lot of studies can be concluded to support growth even if there are adverse events.

The adverse events are a different issue, and I think in the era we're heading into, the DSMBs are critical to any study that's conducted and to be able to have the opportunity, with Brad Skipperman's support, to make really superb independent DSMBs that are taken out of the institution for infant formula studies protects everyone. So I would strongly recommend that.

The issue on adverse events, I think that they need to be-- I agree with Dr. Stallings that the adverse events of interest may be more minor issues and that these all should be addressed as much as possible before the study is actually started, but they need to be monitored and reported back.

And regarding post-marketing adverse event reporting, I as a clinician, and I feel silly not knowing this, I didn't know that there was really a mechanism for even reporting every time I suspected an adverse event, and as a result, I didn't even think about reporting adverse events that could have been related to formulas, not that there ever

were any, but it was not even on my horizon.

So I think having the standardized mechanism such as is available for drug reporting, to get it to be more of a public issue that most clinicians are aware of, would be very helpful.

DR. GARZA: Okay. Any points of clarification, comments?

DR. DWYER: Just a small one, the notion of independent board, whether it's data safety or whatever. To the best of my knowledge, you still have to have the ones in the institutions, so it would be an extra one--

DR. THUREEN: That, I think, is--you can probably answer it better than I can, but at our institution, it doesn't have to be an institutional data safety monitoring board. It has to be a plan with a specific monitoring board, and so in some cases would obviate the need for a local board.

DR. HEUBI: I would concur. That's correct. That is, if you have a DSMB for a multi-center study, centers will accept that as their DSMB.

DR. DWYER: It depends on where you are.

DR. HEUBI: Well, but that's generally what's accepted in terms of--and we've been in sort of a groundswell of this with the GCRCs and that's been generally what's been accepted.

DR. GARZA: GCRCs are General Clinical Research Centers. Dr. Stallings?

DR. STALLINGS: Clarifying, Dr. Dwyer, if we have these outside boards, we're still required to notify in the same timely fashion our IRB; if it's a general clinical research center approved study, them, as well. So it doesn't obviate the need to report it locally, but you don't have to have a sitting board for every study. You have to have a plan. It used to, like six months ago, you didn't have to have a plan unless it specifically was called for because of the complexity or the funding source. So most studies did not have formal plans.

DR. GARZA: Again, we're revisiting ground we should have visited earlier. Are there specific--

DR. THUREEN: And I think it's clear, but I think the data safety monitoring board is empaneled or used during the conduct of the study, perhaps could be extended to the pre-marketing period. Post-marketing adverse events may be a central repository of information within the FDA or some other board that's independent of the data safety monitoring board. Their job is done once the study is considered to be concluded. So those would be two different mechanisms.

DR. GARZA: Okay. The third question?

DR. STALLINGS: And the third question, again, I defer to Dr. Anderson's remarks because I think that they were excellently done. I think we have to remember that this question deals with large differences in attrition rates, that large differences are an outcome in themselves, and that this needs to be looked at. I would love to have this kind of help in addressing these issues. To have a body that would help address these issues for large-scale studies, I think would be terrific, and I also think that kind of information would

help make multi-center studies much more feasible and more acceptable because hopefully a lot of these center-specific issues would be addressed by looking at attrition rates.

DR. GARZA: Okay. Any questions?

[No response.]

DR. GARZA: Would any of the temporary committee members want to amend any of the comments they've heard based on information they've received from others subsequent to their own recommendation?

[No response.]

DR. GARZA: I'm going to move, then, to the permanent Food Advisory Committee members. I understand that some of you do not consider yourselves experts in this area. That's why they brought in the ad hoc group. You do have the option of abstaining on any of these questions, but if you do abstain, I'm required to ask you why.

[Laughter.]

DR. GARZA: But you are not required, obviously, to come up with an answer that you feel uncomfortable with or that you cannot elaborate on.

With that, we tried to keep your interventions to the answer that you can be as fully informed by, theoretically, the group of experts that was brought in with greater expertise in this area.

So with that preamble, Dr. Busta.

DR. BUSTA: And I think you were specifically referring to me.

[Laughter.]

DR. BUSTA: As a non-clinician, I appreciate the education I've received in the last day and a half and I think many of you might think I'm presumptuous at even making comments now on this, but I'm going to anyway.

I also appreciated the FDA short course this morning, bringing another set of slides and trying to focus us in on what quality factors are. I thought that was important because as I see our charge, we are to focus on, specifically on quality factors. And then we were told to specifically aim at normal physical growth, and I think that Dr. Anderson has acquired a charge for all

statisticians to give us a good statistical analysis on nearly everything that we do, and I would think just assessing what "normal" is on physical growth would be a challenge in itself.

In focusing on that, I thought that we weren't giving any emphasis on nutrient-specific bioavailability, the various other kinds of evaluations that we could do on a formula to determine if it is the same. As we were told this morning, a new manufacturer, a major change in processing, major change in formulation are the major changes that I'm assuming are evaluated on this and whether something can be used in one place or the other in our charge.

In those major change examples, one was a significant revision, and again, we have these words of significant, and I don't know if that's statistically significant or just a change. I would appreciate someone helping me understand what significant revisions might mean.

I also saw a new processing line as a major change, and to me, I'm not sure what "new"

means, if it's a new process that, in fact, changes the product or if it just happens to be a replicated line. I have problems with some of those changes to evaluate.

We're talking about, as I saw it this morning, providing assurances prior to marketing of no changes, and to me, it would seem to me that we could have some important, well tested biological analysis that would give us results and not necessarily have to do certain clinical tests if we could demonstrate that those changes in formulation or whatever had not changed the product.

DR. GARZA: Let me clarify. We're not being asked right now to comment on the adequacy of the quality factors issue that we've heard. It's these specific questions. I'm not clear--

DR. BUSTA: But we're being asked to say whether we have a clinical trial.

DR. GARZA: No, it's questions one, two, or three, and if--because if, in fact, we want to go back to the presentation and ask the FDA to clarify, that should have happened earlier this

morning. I'd like you to address one, two, and three, if possible. Otherwise, it's going to be difficult in terms of dealing with the rest of the committee.

DR. BUSTA: All right. I would like to say that one of my favorite comments is that no generalization is 100 percent true, and that includes the one I just said, and I heard that this morning and I think that that is a pretty standard belief and it seems to be consistent with my opinion that a generalized approach that is being proposed that would cover these changes does not seem to be able to be supported, and we've heard all through the last day and a half about this is abstract and it's conceptual and it's non-specific and I would guess as scientists, we have a problem with something being conceptual and then making a generalized assumption.

My preamble was to indicate that I think to determine whether these tests are relevant or not could come in other ways besides the clinical to determine if we can make these justifications

and make these changes, a change in formulation one way or the other.

Consequently, if we're talking about when to do a clinical study or not, I would say that it needs to be--it would not be necessary if it could be justified in good biochemical, biological, bioavailability research. Otherwise, it would need to be assessed.

DR. GARZA: Okay. So that speaks specifically from one product to another or from one population to another or both?

DR. BUSTA: Either one.

DR. GARZA: Okay. Any questions of Dr. Busta?

[No response.]

DR. GARZA: Okay. Number two?

DR. BUSTA: Number two, I'd like to state my how far is it to New York or--I'd go by air.

[Laughter.]

DR. BUSTA: I think that the adverse aspect seems important but I don't know how that is addressed in normal growth. If that's part of the

study and it is the design, then it should be reported and included. Otherwise, we're talking about another aspect. So, again, I would think it could be part of the design, but if it's adverse, it should be adverse on normal growth because that's the charge.

DR. GARZA: Okay. Any questions?

[No response.]

DR. GARZA: So the rationale is because of the narrowness of the charge in terms of normal growth, not because of other physiological or--

DR. BUSTA: And--

DR. GARZA: So it's procedural in your mind?

DR. BUSTA: Yes, and the adverse that I heard some people talk about was that it influences--the adverse events influence the normal growth. So if that's that, then it's a part of the study.

DR. GARZA: All right. Number three?

DR. BUSTA: If the study retains its statistical significance, then the attrition would

have no effect. If you lose the statistical significance by attrition, then the study has to be reevaluated.

DR. GARZA: How would you address the issue of randomness that's been brought up, in terms that it loses its randomness, as well?

DR. BUSTA: Again, if the attrition was matched, then it's random. If the attrition is abnormal and it loses the randomness, it loses statistical design and it's hard to make a decision.

DR. GARZA: Okay. With that clarification, are there any other questions?

[No response.]

DR. GARZA: Let's move to Dr. Downer.

DR. DOWNER: Goulda Downer. I guess we recognize that overall health issues of the preterm infant with a low post-conceptual age differ significantly from those born later and even still those born at full term, and so the nutritional, the metabolical, even physiologic needs differ, say, from a neonate at 24 weeks compared to one at

30 weeks, and even one at 38 or 40 weeks.

Based on that, then, I think it will be difficult in my mind to make inferences to such a vulnerable population with regards to the product of the population itself. That being said, though, I think that perhaps under certain conditions, perhaps with good statistical measures and where the clinical trials may not be adverse to the group tested that some inferences may be made.

My response is a strong iffy one, not a strong yes and not a strong no.

DR. GARZA: Can you elaborate a bit on the criteria that you would then advise a strong yes or a strong no?

DR. DOWNER: I think for me a strong yes in terms of, yes, go ahead and make the inference, is, for example, if in the preterm infant who would need to have--limited to strong no first. If, for example, in the term infant, if additional vitamin A were to be added to a formula, I would say no for the full term and yes for the term. However, the--

DR. GARZA: You mean yes for the preterm

or--you said full term and--

DR. DOWNER: Yes for the preterm. Yes for the preterm. Additional vitamin A, yes for the preterm, but for the term, absolutely not.

I think for my strong no, I would have to give that more thought. As I read the literature in preparation for this body, I wasn't able to clearly identify instances where clinical studies that were done on term infants, for example, could be--the information could be extrapolated and used definitively in preterm. I'm not saying that it is not possible. There may be studies on it or it may come in the future, but so far, I'm not comfortable saying yes for that.

DR. GARZA: Okay. Any other questions or points of clarification?

[No response.]

DR. GARZA: Question number two?

DR. DOWNER: Question number two. I think I concur with the panel in that we would need to have some discipline-specific advisory board or group to help us identify adverse events. I, too,

read this and thought these were two questions. It was not just one.

Adverse events may simply mean no additional growth, if that's what we're looking at, to the end would be perhaps death. Along that spectrum, what is it we're really looking for with respect to adverse events? I think we really would need to get a panel together, not necessarily for post-market surveillance, but I think, again, as Dr. Stallings says, before the study goes even further to the FDA, get a body together to define, to identify, to help make sure that we know what's going on before, because I think when we operationally decide and also identify what we're talking about where we look at adverse effects that it will be much clearer. So I think a panel will best serve that question.

DR. GARZA: All right. Any questions or points of clarity?

[No response.]

DR. DOWNER: I think everybody said Dr. Anderson answered this question well, and I, too,

will agree. He gets kudos for that.

I think with all the statistical measures that should go into a clinical study--I'm talking about the rigorous aspects of it--that the sample size should be large enough at the start of the study to ensure that the sample size remains adequate to detect significant differences, even with the high attrition as we know with human studies.

I think, though, with a large difference in attrition between groups that we probably may not only want to look at the design of the study, but also look at that again as a possible outcome measure, and again, I think a statistical panel would best serve to address that issue.

DR. GARZA: So you're suggesting, then, the appointment of two separate panels, one to look at safety issues and one the statistical rigor of the studies?

DR. DOWNER: I surely do.

DR. GARZA: Okay.

DR. DOWNER: I surely do.

DR. GARZA: Any other points of clarity?

[No response.]

DR. GARZA: Thank you, Dr. Downer.

Dr. Dwyer? It's nice. This group is sort of lined up.

DR. DWYER: Just to preface, I find it difficult to provide responses to general principles and questions that seem to be generated by specific cases. It's just the way my mind works. I'm not very good at The Ten Commandments and I'm not good at this, either.

[Laughter.]

DR. DWYER: I have a little expertise and only very tentative suggestions on processes and panels and the most appropriate ways to go from that respect.

In response to the first question, A, B, and C, in general, no. Generalization is strongest from clinical studies that are done for conditions of intended use, of course, to begin with, and when exceptions are made, and I think there should be exceptions, the burden of proof rests on the

manufacturer. So to protect the public health, the answer is, in general, no, but there are exceptions.

The relevance and generalizability depends on a number of factors, the type of nutrient and all of the other things we've discussed and these need to be considered.

The appropriate generalization depends on the growth response to be measured, that is, whether it's some kind of a core and very broad measure of growth, such as weight, height, head circumference, or more specific types of growth measures, such as maturity or visual acuity or something that's another kind of growth that's measured by other markers and evaluated by appropriate experts.

The special case of very low birthweight, low gestational age infants in non-exempt situations where many may be ill and research on the nutritional or growth characteristics associated with various formula also needs to be studied, but it seems to me that that's at the

basic research level and that this is a very important question and that we need better answers than the idiosyncratic, well meaning but idiosyncratic views of the attending physicians that now often govern the feeding of those infants.

With respect to growth in height, length, weight, and head circumference, generalization, in general, generalization for these exceptions when they occur from preterm to term is more likely to be appropriate than from term to preterm because of the physiological realities that have already been mentioned, as well as the biological continuum of sick/well. So comparisons from healthy to ill or diseased to healthy seem to be more problematic, but I think it depends on the substance that one is talking about. For example, for an emulsifying agent or something or a trace element, it might be very different than for something else, so it also depends.

DR. GARZA: Any questions, points of clarity?

[No response.]

DR. GARZA: Number two?

DR. DWYER: Question two, I think the answer that I can give there is, in general, no, but there are exceptions in that the burden of proof rests on the proponent, the manufacturer in this case.

In the future, major clinically significant adverse events, and I guess the kinds of things--hospitalizations and deaths, of course, but other things, maybe asthma, I don't know because I'm not an expert in this field--are best defined, of course, prospectively and monitored as sort of like with an independent data safety and monitoring board. What "independent" means, I cannot define and I leave it to better minds to do that. But the notion is that the people are not influenced either way by the results of the trial. They have no interest in that on an ongoing basis.

In reviewing existing studies, that is, studies that are already here and finished with adverse events, the first thing, of course, is to define exactly what's meant by that. What are we

talking about? Are we talking about colic or are we talking about hospitalizations?

And when they're disproportionate in the cases, particularly, an independent expert review may be helpful in deciding whether and what should be done and whether the comparisons have been compromised by this. The critical issue is to determine if the adverse events, differential adverse events are caused by the food, the formula, and how frequent and severe and biologically plausible these explanations are.

DR. GARZA: Any questions?

[No response.]

DR. GARZA: If not, we'll move on to number three.

DR. DWYER: The third question, the answer is, in general, no, but there are exceptions, and again, the burden is on the person who wishes to sell the food or the formula. Dr. Anderson, I think, answered that well. High attrition rates of 25 percent in studies such as referred about are troubling and introduce uncertainties and every

effort should be taken to minimize these by all possible means, and, of course, studies should be powered to allow for attrition.

The critical issue is to determine whether the differences in attrition are due to the intervention or to other causes, chance or whatever. The reasons for attrition and also the characteristics of those need to be investigated, and at the very least, it is critical to document the reasons for withdrawal to be assured that the intervention was not responsible. This kind of judgment is probably, again, best made by independent experts.

The other possibility which I throw out in an uninformed way is that one could perhaps do intent to treat analysis, but I don't know if that would get you very far.

DR. GARZA: Any questions?

[No response.]

DR. GARZA: All right. Dr. Hotchkiss, question number one?

DR. HOTCHKISS: My opinion on question one

is the answer is no. I believe that should be FDA's default position and the reason for that is that as the agency's default position, it puts the burden back on the industry to argue why that answer should not be no.

In the case of generalization from term studies to preterm studies, again, in my view the answer is clearly no, not acceptable. However, for other situations, for example, generalizing preterm to term, product reformulations, product crossovers, one crossover to another, a mechanism ought to be available to the industry to have each case reviewed on a case-by-case basis. If the affected industry can demonstrate through scientific studies and independent reviews and reviews of that data that such generalizations are valid, then FDA would be in a position to consider those when it decides whether it wants to accept those opinions or reject those opinions. However, FDA is ultimately responsible for making those opinions or those judgments. However, in some cases, industry should have that option.

DR. GARZA: Any questions?

[No response.]

DR. GARZA: If not, we'll go to number two.

DR. HOTCHKISS: Again, my answer is no, unless an independent panel agrees that attrition is not related to the study and not as--

DR. GARZA: Attrition or adverse effects? I'm sorry.

DR. HOTCHKISS: I'm sorry, adverse effects. Independent review panels and FDA should make aware of adverse effects as soon as possible during any trial. The independent review panel should be responsible for determining if the event is hypothesis related or not. FDA should consider the frequency, type, severity of the adverse event whenever considering any infant formula.

DR. GARZA: Okay. Any questions?

[No response.]

DR. GARZA: If not, number three?

DR. HOTCHKISS: Again, my answer is, no, it's not appropriate when attrition rates are

significantly greater in one group compared to the other. It's very likely that these attrition rates are hypothesis related, and unless an independent review group provides FDA with evidence that they were not treatment related, then FDA should take these into consideration when considering the issue.

DR. GARZA: Are you suggesting that ought to be the purview of the safety monitoring board or independent board or two separate boards or two separate groups?

DR. HOTCHKISS: I do not believe that you need two separate boards, but I do not have direct or sufficient experience in the area to say exactly the mechanism. That should be left to clinicians who practice in this area.

DR. GARZA: All right. Any other questions?

[No response.]

DR. GARZA: If not, Dr. Montville?

DR. MONTVILLE: I have a qualified no to all of these on the basis of sound science, which

says you don't extrapolate to different conditions. However, I do think that there should be mechanisms for the manufacturers to state or to make the case that these aren't different conditions, they're really the same, provided that they are based on science or physiology.

I agree that a board may be useful here, but would suggest that we don't mandate a board. Some of these may be so black and white that FDA could decide it on its own, so we should empower FDA to make that decision.

With regard to question two--

DR. GARZA: Hold on just a bit. Let me see if anyone has any questions on your response to number one.

[No response.]

DR. GARZA: All right. Number two?

DR. MONTVILLE: With question two, as has been noted, there are two parts of this question. If there are differences in adverse effects, those should be examined and followed up and something done about that.

However, even given a real difference in adverse effects, if those adverse effects don't affect normal physical growth, I don't see why the normal physical growth data would be invalidated by the adverse effects, unless I'm missing something here, okay.

DR. GARZA: Any questions? Yes, Dr. Stallings?

DR. STALLINGS: In response to that, if the adverse events that were different were difference in level, say, of diarrhea or food-related allergy but the child, because of the intake, was able to growth through that and, consequently, the physical growth wasn't affected, that might be an example of growth going ahead at a normal rate but the adverse event might be related to exposure to the study formula.

DR. MONTVILLE: That, I understand, that the adverse events should be investigated, but as an adverse effect, not as to relating to physical growth.

DR. STALLINGS: I thought when you had

closed--I was just trying to come up with an example of where I think children often can growth through illnesses--

DR. MONTVILLE: Right.

DR. STALLINGS: --and this particular set of events might be related to the product that we were examining, just as an example.

DR. MONTVILLE: Okay.

DR. GARZA: All right. Are there any other questions or points or clarity?

[No response.]

DR. GARZA: All right. Number three?

DR. MONTVILLE: Question three, I also agreed with most of the panel that the attrition rates can be an outcome to the study, but there should be an opportunity to make the case that they're not. If the industry can provide data that in this particular case, all of these people left town because they worked for the same company which closed, then it's a no-brainer. That should be acceptable. But generally, it has to be, I think, considered that the attrition rate is linked to a

difference in the formula.

DR. GARZA: Okay. Any questions?

[No response.]

DR. GARZA: If not, we'll move on to Dr. Russell. Question number one?

DR. RUSSELL: Question one, number one is presumptively no with the realization that there could be exceptions. I think the final answer on an individual basis could depend on the setting up of a matrix by FDA or by a panel of experts that FDA calls together to look at possible translatability of the data to other populations. The matrix, as I said, should be designed by an expert advisory committee external to FDA, and I think it could be set up with recommendations for specific scoring cutoffs for use by FDA. It's been done before.

DR. GARZA: And that matrix would apply to term/preterm, diseased/health, I mean, the various scenarios?

DR. RUSSELL: Yes, but I think the question was really about term/preterm. If it's

late preterm, for example, it might be more translatable.

DR. GARZA: Any questions?

[No response.]

DR. GARZA: All right. Number two?

DR. RUSSELL: Question two, no presumption of yes or no. The answer depends on the judgment of an independent board, which should consider factors such as biologic probability, severity and frequency of the adverse events and other factors.

DR. GARZA: Can you amplify a bit on what you mean by an independent board? Is it pretty much in keeping with what we've heard, or--

DR. RUSSELL: Yes.

DR. GARZA: Okay.

DR. RUSSELL: And question number three--

DR. GARZA: No, hold on. Let me make sure everyone is as clear as I am on your response.

DR. RUSSELL: Sure.

DR. GARZA: Any other questions?

[No response.]

DR. GARZA: Okay. Number three?

DR. RUSSELL: Question number three is presumptively no for the reasons also stated by Dr. Anderson.

DR. GARZA: All right. Dr. Sigman-Grant gets the last word.

DR. SIGMAN-GRANT: The last word, okay. I'm on this panel as a representative of the consumer and I take that role very seriously. I think a lot of the assumptions are that the caregiver or the person feeding the child is going to be the same, and I would suggest that preterm infants, even late preterm infants, may not be treated in the same manner as term infants and, in fact, that growth can be affected by the person who's feeding, and if some of the clinical trials are done in control settings or with preterm babies, the outcomes might be different in a term baby.

So I'd just like to add that to the presumptive no that everybody else has suggested. It's something I think that's been left out of the discussion and needs to be included, and that would

refer to healthy/diseased, preterm/term, and perhaps even product/non-product because of the difference in intended use and the difference in treatment between potential populations.

DR. GARZA: So am I correct, then, in assuming that you would agree with other reasons that have been given--

DR. SIGMAN-GRANT: Yes.

DR. GARZA: --or would that be your only reason--

DR. SIGMAN-GRANT: No, I agree with the other reasons, but I'd like to include that as an additional reason because I think it's significant.

DR. GARZA: Any questions for Dr. Sigman-Grant on her response to question number one? Dr. Dwyer?

DR. DWYER: So would that imply, Madeleine, that you would like to see studies reported, brought in with that information in them?

DR. SIGMAN-GRANT: No, I just think that it's two different populations--

DR. DWYER: I see.

DR. SIGMAN-GRANT: --and that the feeding may very well be different and growth is dependent on feeding.

DR. GARZA: All right. Number two?

DR. SIGMAN-GRANT: I think I agree with everything that's been said.

DR. GARZA: Could you be more specific?

[Laughter.]

DR. SIGMAN-GRANT: No.

DR. GARZA: Does that mean yes or no?

DR. SIGMAN-GRANT: I think there needs to be an independent board. I think that what has worked in the past, and the industry has done a very good job in monitoring, may not apply anymore because so many changes have been made to independent research and to university research, that the need for an independent external panel is necessary in order to determine how the adverse effects may be different and may apply, and the same for number three.

DR. GARZA: Any questions to Dr. Sigman-Grant on her response to question number two?

[No response.]

DR. GARZA: Number three?

DR. SIGMAN-GRANT: And I, too, would say number three, and refer to both Dr. Anderson and Dr. Hotchkiss.

DR. GARZA: Okay. Any questions?

[No response.]

DR. GARZA: If not, would any member of the panel, of the voting members of the panel, want to amend any of their comments based on what they've heard this morning since they voted? Dr. Dwyer?

DR. DWYER: I'd like to amend mine to endorse Dr. Russell's suggestion of sort of a checklist, which is what I gather you were getting to, rather than always having to convene a group, because remember, the only--if infant formula is like a drug, it doesn't have the profit margin of a drug so that these things can get rather expensive.

DR. GARZA: Okay. Any other comments? Dr. Stallings?

DR. STALLINGS: One clarification. When I

had made my suggestion, it was that there be the case study and that the independent board be there for discussion of situations when after--it's pre-review, and after the industry and the FDA did not agree that there would be a third body to go to, so that not every proposal would require review in a pre-review setting.

DR. GARZA: Okay. Well, I want to thank the group. I hope FDA has found these exchanges to be as informative and helpful as I think they have been. The group has worked extremely well together. We were able to get through the assignment in the prescribed time, and that's a real credit to both your discipline and the fount of knowledge that you bring.

SEVERAL PARTICIPANTS: And the chair.

DR. GARZA: I want to thank you for discharging your duties well in the interest of the public, and I assume that the ad hoc group will be getting together and will be getting back to you with some straw men and possibly some dates in the future.

So with that, unless there's any other business to be conducted, the committee meeting is adjourned. Thank you very much.

DR. TAYLOR: On behalf of the agency, we'd like to thank the panel and the chair and we did find the discussions very informative. Thank you.

[Whereupon, at 11:30 a.m., the meeting was adjourned.]