Dr. Hotchkiss is on the list first.

DR. HOTCHKISS: Thank you, Mr. Chair, for a very nice syllabus for Immunology 101 in your list there. Although I think those are important questions, but particularly for the contemplated uses, that is, as either supplements or functional foods, I am not so sure that those are the major issues.

I guess the first issue, if I were FDA, probably on my list would be history of use of the organism. I think that is a key issue. Things like infectivity, purity of the culture, what care is taken to make sure for purity of the culture, genetics stability, metabolic byproducts of the culture, and are those metabolic byproducts included, are they known, particularly things like proteins which may cause allergenic responses, potential drug interactions.

We certainly know that some fermented foods do have drug interactions. What is being replaced in the diet. We only eat about 1,450 pounds of food, so if you are going to eat a new probiotic food, you are going to take something out of your diet, what is that going to be. Typically, people, at least on a worldwide experience, the Japanese, for example, regularly consume this, so they will take something out of their diet. What is being added to the diet.

We have had the opportunity to taste some of the

Japanese things, but you will find out probably sucrose or fructose consumption goes up tremendously because these things are syrupy sweet, so there is certainly implication to that.

It seems to me those are, at least as a first cut, some of the issues that FDA would want to put on their checklist. Many of the things that you mentioned, I would put under the category of both efficacy and mechanism of action. Many of those things, particularly that I think relates to what kind of claims you want to make, and you have to establish efficacy and some investigation into mechanism, as well, and I would put those in a little bit different category than a lot of the safety issues.

DR. BENEDICT: Thank you. I am grateful for the additional things to deal with safety because that is really important. What we would like to continue to discuss is what you finished with, which are the potential health benefits and what can FDA ask about health benefits.

Dr. Clydesdale.

DR. CLYDESDALE: A rather simplistic approach. I think the common elements I would consider is the mode of action, the marker used to measure the mode of action, and the relationship of that marker to whatever health benefit is being claimed, and then the scientific consensus or scientific agreement as to how valid that relationship is.

Those are the elements that I would consider.

DR. BENEDICT: Dr. Russell.

DR. RUSSELL: Within the mechanism of action would come up whether or not the organism had to be viable at the particular site in the GI tract, for example, if it was an immune stimulatory effect that they were talking about and it was important that the organism be viable, and they would have to know that the viability was, in fact, in the GI tract, that it survived the violence by the acid.

DR. BENEDICT: Dr. Cohen.

DR. COHEN: One of the issues we spent a great deal of time talking about is the identify of the organism, and both you and Dr. Hotchkiss touched on the issue of the characteristics of the organism.

I think there needs to be some thought about that, not necessarily something that we have to discuss in great detail now, but FDA should give a lot of consideration to.

We briefly touched on antimicrobial resistance, and Dr. Sanders might want to make some comments about the general characteristics of the strains that are currently used, but one could easily conceive that there would be a great deal of desirability to having certain drug resistance characteristics.

For example, if you wanted to have a strain that was particularly effective against antibiotic-induced

diarrhea, having strains that were intrinsically resistant to some of those antimicrobials might make a lot of sense. You have beta-lactamase and a few other things.

So, then, you raise the issue of does the use of those types of organisms in large amounts, in large exposure, represent any type of a potential safety issue. So, I think characterizing the organism, as well as identifying those I think is a fairly critical issue.

DR. BENEDICT: Ms. Richardson, did you have a comment?

MS. RICHARDSON: Yes. I am looking at the original question and you ad-libbing about the prioritization of the agency in looking at what approaches and methods are needed to evaluate the potential health benefits.

I think if we are talking about prioritization and also acknowledging that everyone has said there is not a lot of data out there already, is to make sure that the priorities of the agency can be supported datawise by looking at the sister agencies, at NIH, especially since the issue of special populations keeps coming up.

Specifically, NIAMS, the remark about the rheumatoid disorders, but also the Center for Allergy and Infectious Diseases, but also the newer Agency for Alternative Medicine, because in the consumer's mind, when

you talk about nutritional aspects of disease prevention and health promotion, and even treatment, that is what nutrition is seen as an alternative method. So, certainly you would want to make sure that if this is going to become a priority of the agency, that it can be supported datawise, and specifically looking at the sister agencies.

DR. BENEDICT: Thank you.

So, is everyone comfortable with Dr. Clydesdale's List? Do you think we are missing anything by mode of action, biomarker, and readout?

Dr. Clemens.

DR. CLEMENS: I think academically the comments that Dr. Clydesdale made are fairly interesting. The fact is that out of the almost 200 studies that I have reviewed over the last 30 years, biomarkers clearly have not been identified, mode of action have been very subjective, and there might be some association with the strain and a potential health benefit or a potential claim.

But certainly as we have discussed viability today, if we can't agree on viability, how could we agree without validity of the biomarker?

DR. BENEDICT: Dr. Clydesdale.

DR. CLYDESDALE: I guess the reason I raised that is that if we can't agree on the validity, maybe then we must limit our comments as to the benefit of the

microorganism to its effect on structure function. In that way, we can say the marker we used and what is the effect on that marker, and don't imply particular health benefit if we can't relate that marker to the health benefit.

DR. BENEDICT: So, the enthusiasm for the topic of health benefit seems to be less than the enthusiasm for the topic of viability.

Dr. Clydesdale, please.

DR. CLYDESDALE: I don't think it's a lack of enthusiasm. I think every case is different, and I think that if someone is going to make a statement, then, they have to go through this little list we just talked about and present that evidence, that data to the FDA, understanding that the plural of anecdote is not data, and just having something in there that talks about markers and what kind of a claim they are making, whether it be physiological function or whether it be a real health benefit.

So, I don't think it's a lack of enthusiasm. I think it is just that for every specific case, those are the questions that have to be answered, and they are going to differ for every specific case.

The marker is going to differ, the mode of action is going to differ, and whether there is a relationship that is going to differ, and I don't think that we can discuss every individual case and what each of those things is going

to give rise to. I think they have to be treated individually.

DR. BENEDICT: I understand your point, but let me just sort of rephrase. If there are two categories of substances, one like yogurt. Of course, there are some defined benefits at least in the opinion of consumers, but, in general, have been around a long time, and people just eat it because it's good for them, and that is their reason, compared with something that someone says if you take this, we will blunt that case of diarrhea you have got.

What you are saying is that in the case of what is technically a health claim, we have covered that, no problem, right? If you make a health claim vis-a-vis diarrhea, there are certain things you have to do, as you have said.

But what about these things where people don't expect to make a health claim, and we are going to suggest a physiological effect that has no further definition than that, so what does FDA do when it says we will make you feel better if you eat our organism?

Is that a health benefit or is that not a health benefit? Is that something that they need to ask questions, what is the definition of "make you feel better," and I don't mean to make this really simplified, but for me I have trouble with that because it is sort of a fact, isn't it,

that things we ingest to make us feel better are going to be classified as probiotics, and if that is the case, does the FDA ask for something concrete, and if they can't see something concrete to ask for, does that make this not a probiotic?

Please respond, Dr. Clydesdale.

DR. CLYDESDALE: I just don't know how I would show whether it makes me feel better or not. I think I would probably go right to the endproduct, the alcohol, but I think that if you wanted to be a little more specific than that, one could talk about, you know--and I think rightly so--maintaining an healthy intestinal tract, and the marker could be, the marker you used to say that could be something as simple as talking about the number and types of microorganisms in the intestinal tract.

DR. BENEDICT: You opened a can of worms with that. Would anyone like to respond to that statement?

DR. CLEMENS: I will take a try. I have seen changes of one to two logs, which may be statistically significant, and you can see a decrease of one or two logs of Bacteroides across strain, for example, and increased logs of one or two, and Lactobacillus bifidobacteria, for example. In some studies, they show, depending on your outcome, there may be a positive outcome, and then again, there isn't any change whatsoever.

I have seen other studies to look at metabolic byproducts, for example, short chain fatty acids that Dr. Grant referred to, and some show a micro change of fatty acid and pH change, and others show no change, so it depends on what your population is.

My sense of the literature, however, is that particularly in pediatrics--and I appreciate Dr. Fukagawa's comments--that it appears that the more compromised the subject is, or the study subject is, the easier it is to detect a potential benefit.

Having studied many populations that are "healthy," it is difficult to identify a healthful benefit in that population group.

DR. BENEDICT: Dr. Hotchkiss.

DR. HOTCHKISS: I wanted to agree with Dr. Clydesdale's earlier comment you have got to take this on a case-by-case basis depending on what claim you want to make. If you don't make any claim at all, then, you put it in, then, it falls under the rubric of general safety, and so forth, and there is plenty of area to cover that.

If you make a broad claim or a claim, let me think, of something related to diarrhea1 disease--not to diarrhea1 disease--but promoting healthy GI tract or whatever, there is a certain set of criteria for that.

If you are going to make a claim of

immunostimulation, probably you need a lot more, and a lot more detail for that particular claim, so it is hard to broadly paint a requirement around this for efficacy without saying what the specific claims are, and specific claims, of course, then, are going to categorize whatever your substance is, as different kinds of substances or different categories within the law.

But the degree of detail I think really does relate to the kind of claim that you are making about it. If you are going to make an immunological claim, then, probably you are going to need a ream of data. If you are making no claim at all, you may not need any data at all.

DR. BENEDICT: Dr. Russell.

DR. RUSSELL: Well, the problem is there is no criterion for a healthy GI tract that is set down, and that is the crux of using that kind of language, is that it is just fraught with doctors just dismiss that and dismiss the whole concept, I think, of probiotics having anything to do with that, because until there is real hard data showing that it does, in fact, have some functional effect, it is not going to be accepted.

I think that is a problem we are in now, is that we are using this vague language or what is being used is just sort of vague language about a healthy GI tract or floral balance that doesn't mean anything to anybody from a

clinical point of view.

DR. BENEDICT: would you like to respond?

DR. HOTCHKISS: I just want to respond I couldn't agree with you more, you are absolutely right. That gives FDA, in my view, that is what FDA should come back with on that claim is that there is no medical agreement to what this particular claim may or may not mean, and until you can convince us that it is important.

DR. CLYDESDALE: On this topic, I would just completely agree with what Rob said. I gave that, not as an example of what it does, I gave it as an example of the kind of claim that would have to be proved, and if can't be, then, you don't get it. It's as simple as that.

DR. BENEDICT: Exactly why I always enjoy your comments, because you say things people get to discuss.

Dr. Gaskins.

DR. GASKINS: I don't want to interrupt the momentum here as it takes off, but just one comment related to the healthy gut, and I don't think this came out well yesterday. An additional advantage of molecular approaches in which you can define community profiles is that now it is possible to survey a number of individuals, say, within a treatment or within a certain population.

The overall finding there is that population profiles vary widely among individuals, very stable within

individuals, but vary widely among individuals. We are also doing this with inbred mice, genetically identical mice that we brother-sister mate, and find surprising differences in genetically identical mice that had the same diet, the same light/dark schedule, and so forth, and so on.

So, I think, just to reiterate, that indeed it will probably never be possible to define a healthy gut as to being comprised of a certain population or community profile of bacteria, because it seems to be quite varied.

DR. BENEDICT: Thank you.

Dr. Fukagawa.

DR. FUKAGAWA: I guess the way that I look at it, that is a little confusing, on the one hand, we are talking about acceptance from a clinical standpoint or a practicing physician or a health care provider in terms of how he or she would support the consumer's perception of what this ingestion of a material will do for them.

That is where I think we run into some problems because in many ways, going with Dr. Clydesdale's approach, in terms of defining the organism, then the mode of action and the efficacy is great for all of us, but yet, there are a lot of people out there who would not care at all that we knew how it worked except that it made their gut healthy or whatever that means because who knows what healthy means, because it will be at the level of the consumer.

So, I guess my approach would be from the standpoint of starting with what we would know, namely, what is industry claiming for that particular product, and for that particular product or probiotic, what is the organism, what is known about the organism, either historically or experimentally, in terms of its effects, and then going along the lines of the safety issue, and then potentially the mode of action, and only sort of certify or approve a claim where we can substantiate that it does have the outcome that we are proposing that it should have, because otherwise, I think we tend to get very confused information into the public arena, which they won't know, so then they will just say, oh, God, these nutrition people just don't know what they are talking about again, because, you know, they are saying, on the one hand, this is okay, and this isn't, tomorrow, we will change our minds.

So, I think as much as possible, given the information that we do have from all of the microbiologists, we should look at strain or organism-specific, strain-specific, then, the phenotype of that organism, and then its proposed mode of action and then effects, and the potential side effects. Went around the circle, but--

DR. BENEDICT: Thank you, and it is circular, but let me go back to if the claim is really not a mode of action, and the claim is really not much of a benefit other

than in some neutral thing, is that something the FDA needs to deal with other than safety?

Dr. Buchanan has a comment, unless you have a response, Dr. Fukagawa.

DR. FUKAGAWA: I guess I am just trying to define, I mean, what do you mean, a broad thing like it makes you feel better?

DR. BENEDICT: Well, this is my problem. My problem is "make you feel better" is still something people are saying. I can deal with all the science that you put before me, but I can't deal with something that the outcome isn't directly defined, and I don't know whether FDA has to deal with this or not.

What I am hearing is no. What I am hearing is if you don't have a defined outcome, don't come to us and let us use the word probiotics.

Dr. Buchanan, what is your comment?

DR. BUCHANAN: What would be the appropriate--if maintaining a healthy microbiological balance is not an endpoint that can be measured or is interpretable--then, what are the outcomes that we should be looking at, and, two, what are the types of analyses or supporting data that would be needed to make those claims.

For example, when people say about maintaining a healthy balance within their intestinal tract, is that a

different way of saying that you will help prevent intestinal disease, then, the obvious question is, is what disease, how do we test for it, do we do human clinical trials particularly if it involves feeding infants?

I mean if you were looking at a vaccine and you were testing the efficacy of a vaccine, what you would do is you would set up feeding trials or some type of challenge. Now, are you recommending that we do the same thing here? If you don't use that term, what are the endpoints that we should be looking at, and what are the specific data sets and the degree of sort of the bar that they need to get over for and toward in order to demonstrate that claim.

Now, we heard discussion yesterday about clinical placebo-based, double-blinded trials. Is that the gold standard that we should be using for any kind of a claim?

DR. BENEDICT: So, let me just add one question to that. Is it sufficient to put 2,000 people on a program where you give them X and you give them a placebo, and at the end of Y period of time, you have accumulated knowledge that they say I felt okay this week?

I don't mean that in a facetious way. I mean that is essentially where we are going. If you have a group of folks with incidence of GI discomfort and lesser incidence, is that sufficient? So, I just want to add that to your comments, so that people can then discuss everything.

Dr. Russell.

DR. RUSSELL: Well, I think it is a problem with structure function claims that FDA has seen so many times on other functional foods and supplements, and so forth, and that is that the structure function claims are oftentimes health claims in disguise, and have cynically been used that way, so that it promotes healthy prostate means prevent prostate cancer even though you can't say it prevents prostate cancer.

But I think that instead of getting around this microbial balance, and so forth, which doesn't mean very much to anybody, that you can talk about perhaps gut immunity, which is a function, or gut barrier function.

I mean I am not sure of the exact words, but I am sure Dr. Gaskins could give us some good ideas on function that we could talk about instead of talking about, you know, promotes your healthy gut flora or something like that, unless you want to say, in an infant, that this helps restore your flora to where you were as an infant. I mean. that was sort of implied yesterday that that might be beneficial.

But as for bowel function, perhaps, you know, that can be empirically tested. I mean, on the one hand, we see that these probiotics can relieve constipation. I would love to look at those studies and whether it is the vehicle

that they are in and the lactose that's in those vehicles that relieves the constipation.

On the other hand, they can relieve diarrhea, and I would love to see those, too. Can they relieve functional diarrhea, which has nothing to do with infection, but is functional diarrhea? These are things that can be empirically studied.

DR. BENEDICT: Dr. Clydesdale.

DR. CLYDESDALE: I would leave questions like these to Dr. Russell, but in another panel I was on a couple of years ago that had some discussions on the intestine, some surveys came out that pointed out that any given instance, 40 to 60 percent of the population suffered from at least some kind of perception of intestinal disorders. So, to do any kind of large-scale study on intestinal disorder is when that is the baseline, it becomes very difficult, but in terms of the other comments, I would leave to Dr. Russell's expertise.

DR. BENEDICT: Dr. Sanders.

DR. SANDERS: To build off of Dr. Russell's comments, I think that, first of all, the concept of a structure function claim and these general type statements that are made oftentimes on products, are a result of the fact that people aren't allowed, companies aren't allowed to make health claims.

I am stating the obvious, but basically, you are sort of forced to make broad, general statements because that is the way the regulatory climate is right now, but having said that, it seems like if a product is being marketed as a supplement or a food where structure function claims are allowable, but health claims are not, the standards should be somewhat different, and I would argue somewhat lower than truly making a drug claim.

So, I think that it all comes down to a continuum or a classification of the quality or quantity of information that needs to be available to support a statement.

Now, having said that, I do acknowledge that promotes GI tract health is a very general concept that is very difficult to get your hands around and to define, but so many of the studies that have been done in the area of probiotics are really focused on certain aspects of that, of which Dr. Russell mentioned, and my list includes translocation or barrier effect, certainly would relate back to a healthier GI tract.

There is quite a few studies of colon tumors in animals, the suppression of colon tumor development in animal studies that may, in fact, be considered applicable to a GI tract health claim or structure function statement. The diarrhea has already been mentioned. Side effects for

lactose intolerance like flatulence and bloating. You know, they have scales to measure that within people, and they certainly have reported statistically valid effects or decreases of those types of symptoms.

I think that, you know, from the FDA's point of view, if someone is going to say GI tract health, there may be a variety of different types of targets that fall underneath that, that would be allowable to, in fact, have evidence to support that more general statement.

But the fact that people are using promotes GI tract health, I think to some extent is largely because that is what they have to do, they don't have a lot of choices if you want to market a food or a supplement.

DR. BENEDICT: Dr. Fukagawa.

DR. FUKAGAWA: Now I am thinking about the consumer. The two groups, healthy groups, that could potentially be targeted for the use of probiotic supplemented foods would be the pediatric age group or the geriatric age group, two groups which we do have to consider are oftentimes economically on a more limited income, have more limited incomes, the elderly because they are, you know, on retirement income which may not be very excessive; the pediatric patient because his or her family may be just starting out and didn't inherit a lot of money from mom and dad, so therefore they have limited resources that way.

By promoting broad, general claims that will affect these two groups who want to do good for their families may be putting them in an unfair position because a lot of times foods that are sold with health claims tend to cost more or may cost more.

If we don't have true evidence that it really does promote good health, then, I think we are misleading the public, and not really protecting them from the potential of abuse because they are going to buy into advertisement along lines which may not make any difference in the long run.

So, that is where I get torn. I get torn with respect as to what to do.

DR. BENEDICT: Dr. Montville?

DR. MONTVILLE: Bob, could I just ask what standard is used for the claims in nutritional supplements.

DR. BUCHANAN: Dr. Yetley?

DR. YETLEY: There are lots of different types of claims. The health claims for supplements, the science substantiation standard, is equal to what is on foods, conventional foods. The structure/function claims, which are specifically mentioned under DSHEA, under the Dietary Supplement Health and Education Act, do not have a formal science substantiation although the claim must meet the truthful not misleading standard that goes across the board for all food labeling information.

DR. BENEDICT: Dr. Hotchkiss?

DR. HOTCHKISS: This brings us back to where Dr. Clydesdale started with us. In order to evaluate this, you have got to look at the claim that is being made and then you see what standard is applicable to that claim.

DR. BENEDICT: Which I think we would all agree with. I think FDA is hoping to hear creative assaults on the process.

DR. YETLEY: Can I just comment on that a little bit?

DR. BENEDICT: Please.

DR. YETLEY: I think the issue, again, coming back specifically to probiotics, what specifically, in terms of evaluating the substantiation for a specific statement, regardless of what type of claim it is, what kinds of information would you need relative to the test substance, the test organism. What kinds of physiological endpoints would you need to be able to have information, the kinds of information, very specific, to a probiotic use? What pieces of information would you absolutely have to have in order to evaluate whether or not the science gives you the relationship that is being claimed?

DR. BENEDICT: This would include things like effective dose, dose response, things of that nature?

DR. YETLEY: Yes.

DR. BENEDICT: Dr. Russell?

DR. RUSSELL: But I would say, Beth, that if you allow this healthy GI tract as a claim, that is so vague as that it would be very hard to give you the criteria on which to evaluate that, if you are talking about--or bacterial nicrobial balance.

I don't know what we could possibly, or anyone could possibly, give you on that. So I would think that you Would, on these GI, at least vague GI claims and some of the other vague claims, is try to make them not so vague and get them to be as specific as possible about the effect on GI immunity, if that is what they are talking about, or the effect of increasing a certain type of bacteria, or the effect on increasing barrier function against possible pathogens.

But I think the vaguer the notion is about GI health or microbial balance, the harder it is to come up with--tell you what criteria to use.

DR. YETLEY: I think the other issue that we haven't touched on to a large degree is how much detail do you need, in the description of the organism, to be sure that what is in a specific product does, in fact, relate back to your available science. If you have a published study and the organism is described in a certain way, is that sufficient, then, to say you can generalize the results

of that study to a specific food product with a certain type of organism and have some assurance that that relationship that the published study showed would also prove beneficial for use of that particular food product.

So how much information do you need to go from a scientific study to a reasonable assurance that a claim that is derived from that study will also be effective when it is actually applied to a specific food.

DR. BENEDICT: So we did, earlier this morning, discuss strain identification.

DR. YETLEY: Right.

DR. BENEDICT: So does that address what you are saying?

DR. YETLEY: As long as you think it is still sufficient. It was more in the context of safety and general. Does that still hold for efficacy issues or do you need more specificity, would be the question.

DR. BENEDICT: I see.

Dr. Russell?

DR. RUSSELL: I think we have said it before, at last one of the issues is whether the vehicle, or the food, that the organism is now in, affects its delivery. If its site and viability is important further on down, then we have to know that the vehicle doesn't affect that in a negative way. That would be, certainly, one thing, when you

put the organism in a new vehicle that hasn't been tested before.

If it is not important that it is dead or not, or that it just reaches the stomach or something, then whatever happens to it in the stomach doesn't matter. The vehicle probably is not nearly as important.

DR. BENEDICT: Dr. Gaskins, we have you on the list. But the suspicion is that the continuation of this discussion might--Dr. Hotchkiss?

DR. HOTCHKISS: I would just. add to the issue of identification of efficacy. It is extremely important, the issue of numbers of organisms so that you don't get claims made on products that have very low numbers of organisms or the culture has been waved by the product in the hope that some fell in, because I think there are those kinds of products out there.

So I think, in addition to the identification-specific organisms, the numbers are very important by serving or whatever.

DR. BENEDICT: Dr. Fukagawa?

DR. FUKAGAWA: In response to Dr. Yetley's comments about knowing what studies or data would be transferrable, I think the quality of the study design would be important in terms of using that as background information to support a claim. But then it also has to

relate to dose and the specific organism and its phenotype.

The other thing that I think should be considered is oftentimes we do studies in normal, healthy people to try to prove efficacy. In certain situations, reducing five bowel movements a day to two isn't necessarily going from abnormal to what is normal because, in an individual, five may be normal.

so how to use that kind of scientific double-blind, placebo-controlled, type of study to support your claim for something where, because of your interest in using that claim, you say that this is an abnormal function is, I think, an issue, especially with GI symptomatology, which is so common.

DR. BENEDICT: Let's go to Dr. Buchanan and then we will go to Dr. Gaskins for his earlier comment.

DR. BUCHANAN: I did want to follow up and sort of reinforce a statement going back to the question of viability and how far you can extrapolate the results from one to another. If you are using a viable organism that is viable within the intestinal tract, it sees the environment of the intestinal tract and you can probably extrapolate using a number of different vehicles.

However, if you are looking at an organism that is viable when ingested but not viable when it hits the intestine, pretty much what you had in the cell is what to

put in your mouth. There, you can have tremendous impact on the expression of different genes, particularly any inducible genes, and the level of the active agents that are actually producing the effect.

There, I would suggest that the matrix that you grow the organism up is very critical and I would suggest that it is not extrapolatable beyond a limited degree where there is the potential for a great difference. Fermenting things in milk is not the same as fermenting things in soy milk. They are different.

DR. BENEDICT: So it just gets curiouser and curiouser. The question of what scientific things we should consider when we are thinking about potential health benefits, health effects, and their priorities, we have raised a lot of questions. We have said some things that, of course, are very trenchant and are effective, but we do still have the question of viability.

We do still have the question of a nebulous claim that people might still want to be able to happily make and should they be able to justify that with something.

So let's just continue to focus our thoughts on this by thinking about what methods we have available to measure them. If FDA is going to address questions, what methods can they use to address them? Maybe this will bring us back to some of the questions about the health effects.

So, among the things we have heard, of course--Dr. Clydesdale raised the issue of biomarkers. We heard yesterday that germ-free animals are very good for certain approaches. Clinical studies are the final arbiter of everything, if you can design one.

But let's not forget that, in addition to clinical studies, there are a lot of animal studies. We have heard and we have read that, as I said probably more times than you wanted to hear, things that do things in animals don't always do them in humans. So how can you extrapolate, in many cases, especially when you are talking about the digestive tract.

So we want to, perhaps, help FDA focus these things and maybe suggest new models. Even if we don't have them, what could we use, what could someone design, what could somebody consider, that might be helpful to FDA. Dr. Clydesdale?

DR. CLYDESDALE: I just wanted to clarify the term "biomarker." I used the term "marker," actually. The reason I did is--

DR. BENEDICT: Sorry.

DR. CLYDESDALE: No; the reason I did is because a biomarker often is immediately associated with a disease endpoint. I used the term "marker" because I was saying that it may be associated with a physiological change and

may or may not be associated with the disease endpoint. That would be the next step, is to show it.

So it really isn't a biomarker. It is just a marker; what are you measuring to show a physiological change.

DR. BENEDICT: Which is even better than what I said.

DR. CLYDESDALE: And then, if you want to go further and talk about reducing the risk of a disease, then you would have to show a relationship and, in fact, make sure that marker is a biomarker.

DR. BENEDICT: Thank you for the clarification. Obviously, that was a big stimulant to thought.

Dr. Gaskins?

DR. GASKINS: I think it just occurs to me that we are having trouble trying to define a healthy gut. Dr. Russell points out, being a gastroenterologist, that term is very vague to him. And then we also acknowledge that 40 to 60 percent of people perceive that they have an unhealthy gut at any point in time.

So it seems like, at some point, we are going to have to--FDA will have to work with their sister agencies to release an RFA to try to define a healthy gut. I think it could be done. I think Dr. Sanders listed a number of criteria that might be included in that, some metabolic

profiles of bacteria, if not particular strains or community profiles, but the soup, so to speak.

So I think that kind of information could be brought together, but I don't think we have it now. So what do you do in that situation?

DR. BENEDICT: I think a request for an RFA is very appropriate. Obviously, that wasn't much of a stimulus to considering health effects, or--yes; Dr. Sanders?

DR. SANDERS: I am getting back to Dr. Yetley's request for a checklist because we have a broad discussion about what are valid markers or biomarkers. That is a very appropriate topic which goes beyond the question of probiotics.

If you want to look for an immune-function claim, whether you are doing echinaceae or probiotics, you probably have to ask the same question about the validity of the marker. But, in terms of the specific probiotic effects, just maybe to summarize, I think that if we are looking at probiotic-specific issues, I think dose, which everyone has mentioned. The number of viable cells is going to be a critical definition point that the FDA should pay attention to.

I think strain identity, and that probably can be defined more but, certainly, there are genetic techniques that allow a pretty good fingerprinting of what particular

strain, and I have to emphasize "or strains," go into something because many times these are multiculture products.

And then, to really emphasize Dr. Buchanan's point, I think it is very critical that anyone providing information or data to the FDA on a probiotic product has to very carefully define the growth conditions; the media, the temperature, the levels of oxygen, whatever, what other kinds of conditions are involved in growing it because, as was pointed out, those are very important characteristics of the expression of the final genes in the organism.

And then, finally, how it is delivered. I think that that needs to be a controlled aspect because how it is delivered is going to affect, ultimately, survival of that organism once it hits the gut or hits the stomach. So those, in my opinion, are the issues that might be probiotic-specific, that might be somewhat different than just delivering vitamin C through a product, or whatever.

DR. BENEDICT: Dr. Sigman-Grant?

DR. SIGMAN-GRANT: I was going to follow up with what Dr. Sanders said, how it is delivered and how it is manufactured, because I think the manufacturing process might be extremely important in the viability and whether a claim that are made about a specific strain is actually appropriate to the end product that the consumer is actually

taking.

I am thinking, again, of the infant-formula issue, so not only the vehicle but the manufacturing, the final end product.

DR. BENEDICT: Let me just amplify a little bit as well. If an organism is proposed and if the strain is well-defined, and the culture conditions are well-defined, really well-defined, is it reasonable to suppose that what goes into the human will be expressing the same factors each time it is done. I think that is not a bad assumption as long as the culture conditions did not favor the outgrowth of some odd mutation, which we probably can't, at this time, look for anyway without, as Dr. O'Sullivan mentioned, sequencing the whole organism.

But on the list of things that we can do, if you talk to people like Francis Collins and wait five years, then we will sequence an awful lot more nucleotides per day than we are now. So it is within the realm of possibility that, in fact, before too long, we can sequence the whole thing--he says, in his science-fiction way.

But, in fact, that is the ultimate thing. Then there is a mutation that you can recognize, start to finish. So something we need to think about is moving in the direction of paying attention to what is happening with the genome, folks, because it will happen. But it won't be too

much more challenging to do that.

So is that a fair assessment? If you have got the right strain, you culture it right, do you need phenotypic characteristics before you go into the organism, or do you make the assumption that it is okay?

DR. SANDERS: I am not sure I understand the question. Are you saying every time you make a batch to phenotypically describe the organism that comes out or can you assume that--

DR. BENEDICT: That is what I am asking.

DR. SANDERS: There are huge industries that are very skilled in being able to grow these microorganisms for food use, different types of food-ingredient production, things like that. So I think the technology is clearly there to minimize the effects of genetic drift, or shift--I forget, now, how it was used. I guess "drift" is the proper term.

I am not convinced in practice that is always done with some of the smaller companies. I think that there is very poor definition of strains going into products right now in some cases, but with the people that have been in business for a long time and have a large enough business to really put some care into their quality control, the techniques are available.

That is not a huge technological hurdle, to be

able to minimize the genetic drift and make a consistent product. So, to answer your question, I don't think that there needs to be a huge effort to phenotypically give huge characteristics every single time.

DR. BENEDICT: Dr. Cohen?

DR. COHEN: In thinking about this, I wondered whether or not there was anything that would be helpful from looking at the past experiences with approving some of the oral bacterial vaccines. You are asking a lot of questions that probably were asked in the past when people thought about typhoid vaccines and some of the others.

So it may be worthwhile for FDA to take a look at what the other part of the agency did with some of those particular submissions.

DR. COHEN: Dr. Clemens?

DR. CLEMENS: Just to piggyback.on Dr. Sanders' comments, I have worked with a number of organisms for many years and worked with outside laboratories to validate the procedures I have in my own laboratory. In fact, several outside laboratories have said, "Roger, we no longer want to test your organism because it is so consistent. There hasn't been any demonstration of changes in bioacid tolerance. There hasn't been any change in genetic makeup."

And so they said, why should we do it anymore because you have very rigorous standards in the production

of your organism. So then it falls back onto whoever is producing it and say they have to develop the methods inside, and that is not very cost-effective. In fact, you have identified a lab that is very clinical, so that may well put some of the manufacturers at odds in terms of trying to redevelop the procedure that they have been relying on outside experts to count on.

I do support, though, the concept that we need a consistent evaluation of the strains and I would encourage us to adopt that procedure.

DR. BENEDICT: Dr. Fukagawa?

DR. FUKAGAWA: One of the difficulties I am having is, in a sense, we are discussing a lot about restoring GI health or trying to define what the broad definition of health is. But, in reality, we are not going to be once prescribing the use of these food supplements or specific foods. It is going to be the consumer.

So it would seem like, although I agree with much of the evaluation and the issues and points that we need to take into account to assure a certain amount of safety and efficacy, what is going to happen is the decision is really going to rest in the hands of the consumer as to whether he or she will believe what is on the package and want some assurance from FDA that they won't hurt themselves if they triple the dose because, somehow, we tend to think that

three times is better than one times the dose.

So although I think we would all agree that we can 30 these fine definitions of what we might be wanting to achieve from a scientific intellectual standpoint, I think we need some feedback from the people who are using it as to whether or not it is making a difference.

If a claim is made, that we do follow it up with a length of postmarketing surveillance, and not just say, "Okay; now it is out there and you decide," because if we put a lot of effort into assuring safety and efficacy, then we should be able to then learn from the people who are using these products.

DR. BENEDICT: Dr. O'Sullivan?

DR. O'SULLIVAN: Just to follow up on Dr. Sanders' question or comments, when you define a processing methodology for preparing an organism, that methodology can be validated for whatever phenotypic criteria are deemed important. And that can be quantified. So, essentially, it is unrealistic and unnecessary to essentially keep validating a methodology each time.

If the process and methodology, then, is changed for some reason, then it needs to be revalidated. But you don't need to revalidate a defined methodology every day.

DR. BENEDICT: Thank you.

So we have reached the point here where we are

supposed to be going to lunch. What we have left to discuss are scientific factors relevant for, perhaps, differing categories of potential health benefits. We have sort of discussed that a little bit already, potential novel uses, additional scientific factors relative to potential new uses, and then see, which is under safety and efficacy, what do you consider appropriate criteria for establishing safe exposure levels and what do you consider appropriate criteria for evaluating efficacy.

So the question here is do we think we can do this in thirty or forty minutes and call it a day. The way it has been going, it is entirely likely we can't, which is fine because discussion is good. So, should we take an hour for lunch and return to finish? We know folks have airline reservations impinging closely on the 2 o'clock time we have set.

So my feeling is we just soldier right on. Okay; we will soldier right on. Some of us have to check out and we can, perhaps, ask for delayed check out, if you like. So, if you do need to check out, please do so or go ask for them to delay the time. And we will just move right forward.

So, special populations. We haven't really defined much beyond special populations other than infants, immune-suppressed individuals and things like that. We

would be happy to entertain them, but it has been two days and those are the ones that we mostly heard.

DR. FUKAGAWA: Geriatrics.

DR. BENEDICT: And geriatrics. Thank you. You did mention those. My fault. Applied? That is outside our purview at the moment since we agreed to limit ourselves to ingestible.

DR. SIGMAN-GRANT: Some of the things are ingested as well as applied.

DR. BENEDICT: Fine. So, an additional population. So we have defined those. Are there additional folks that we should add to the list and, if not--

DR. SIGMAN-GRANT: Specific diseases.

DR. BENEDICT: Yes; any cofactor, any co-disease.

DR. CLEMENS: Do you wish to address pregnant and lactating women as a special group?

DR. BENEDICT: I am asking that question. Add them to the list; absolutely. Perhaps, this is a similar thing to differing categories of potential health benefits if, in fact, what is considered the healthy population responds in a certain way, do any of those folks on the list respond differently? That is essentially the same question said a second time.

But is it appropriate to, or can we think of logical reasons why, we should have different categories of

health benefits? There is the resurrection of the "I feel better" compared with a benefit for something a little more structure/function. Do we need to help FDA by giving them categories that they would then ask, "Do you fall into Category A or Category B?"

Dr. Montville?

DR. MONTVILLE: I think that would be useful because I can see different categories in "promotes," "prevents," for example, "traveler's diarrhea." "Prevents, is useful in alleviating the symptoms of;" that is not treatment, is it? Different categories like that would have different kinds of levels of proof that you would need.

DR. COHEN: Dr. Clydesdale?

DR. CLYDESDALE: Could we have some clarification on what differing categories of potential health benefits means?

DR. BENEDICT: I am sure we can get that. Not having written this, I am sure Dr. Yetley or Dr. Buchanan would love to answer.

DR. YETLEY: I think it actually deals with the different categories you have already talked about where some are for well-being, healthy GI. Some are for reduction of likelihood of diarrhea. Some of them are for immune function. So I think, to a large degree, you have probably already dealt with these.

DR. CLYDESDALE: I thought we had already done it.

DR. BENEDICT: Thank you. We have done it, but we haven't really said what Dr. Montville said; that is, should there be structured categories, or should it be a gradient of things that is just on a case-by-case basis. Perhaps that is what we have concluded, that it is on a case-by-case basis and there really are not specific categories that you go into, Column A, Column B, Column C. That is what everyone seems to be nodding their heads about, so that is wonderful.

Ms. Richardson?

MS. RICHARDSON: To follow up on Dr. Fukagawa's remarks about the postmarket surveillance in talking about the categories of potential health benefits and what needs to be done with those, I think also because, again, we do not have clarity about what the health benefits are. It runs from the nebulous "I feel better" to it actually does do something that can be quantified.

For the consumer, there really has to be an articulation from FDA what benefits are and also to dispel some of the myths surrounding these things that are called diet supplements. I know what the law says, but all of us blanch when we talk about supplements and drugs and is it treatment, or whatever.

So you can imagine what the consumer is doing. So

there has to be some articulation about exactly what the benefits are. Are they definitive benefits or are they a sense of well-being, and lay out what the myths are and what the facts are.

In addition to that, with some of the special populations that are out there, with geriatrics, with some of the minorities that have concerns about the credibility of the nutritional information that they have been getting over the last ten years, that, as has been said before, this would just be some more information that they may want to discount.

In addition, we know that the industry is going to be marketing it very creatively so even if the words are not there, that this will cure your diarrhea, they will think of some way to impart that information.

There are also concerns in some of the special populations, the conspiracy theories dealing with illness, things being put into the water system, into foods, whatever. You are talking about probiotics and bacteria, so I think there is going to need to be some public education about what the benefits are, what the risks are and exactly what this is, and that, yes, we have been eating yogurt for years so this isn't something new.

But, for some of these special populations, especially minorities, they don't talk about probiotics.

Probiotics, I'm sorry, is a yuppie-buppie term. The general population is not out there talking about it. So when they see this, and they see some of the ads that are in some of the hand-out literature, and Dr. Grant has some that is being used in the pediatric community, when they see bacteria being put into food, there are people who will seize on the conspiracy theory of illness or whatever.

So I think that, in addition to looking at postmarketing surveillance, you are also going to have to look at premarketing informational education about probiotics and about benefits and about risks.

Even though these questions were termed in the context of scientific elements, I think that we have to look at the public-education piece and the marketing piece that does not talk about the scientific evidence.

DR. BENEDICT: Dr. Cohen?

DR. COHEN: Just a very quick question. I think you are right on with a lot of these issues here that we look at a scientific level and we don't grasp them with the same-- in fact, I would be curious of anyone has data as to what percent of the U.S. population know there are bacteria in yogurt. Do any of our folks actually know that information?

DR. HOTCHKISS: I don't know that, but I asked between 85 and 90 students that question and I would guess

that two or three knew that there are.

DR. BENEDICT: Dr. Clemens?

DR. CLEMENS: I reiterate what Dr. Hotchkiss just said. I lecture to many women's group and nine out of ten do not know that bacteria exist in yogurt today.

DR. BENEDICT: Unless there are other comments, we will move to the last two questions. What do you consider appropriate criteria or parameters for establishing safe exposure levels? This has to incorporate things done with humans, things done with animals. Maybe there are in vitro questions that can be asked, cytotoxicity and things. What do you consider the parameters that ought to be looked at for safe exposure levels? How can you prevent someone from overdosing on lactobacillus?

Dr. Sigman-Grant?

DR. SIGMAN-GRANT: I was just going to say that, for much of the population, I think it is pretty well-established for some of the organisms, like with yogurt. But for the special populations or for special uses, then I think you need to reestablish those markers. You can't just assume because it is safe for general use and has been used for centuries that it is, indeed, safe for specific populations.

So you would need more defined criteria, say, for a pediatric population than you might for the general

population where you can make claims. So you might add things like growth parameters.

DR. BENEDICT: Dr. Cohen?

DR. COHEN: I think there might be certain instances where you would want to have appropriate animal models, for example if you are dealing with an infant model or if you are dealing with a compromised host model. That might give you some indication where you have some degree of suspicion that there may be a potential difference in the population or the risk.

That might be helpful in confirming a lack of an effect or an effect.

DR. SIGMAN-GRANT: Can I ask a question?

DR. BENEDICT: You raised the point.

DR. SIGMAN-GRANT: We are talking about models. Were pigs used in any of these studies because I have heard that the pig is very much a good model for a human, or at least the piglet gut. Does anybody know?

DR. RUSSELL: There are characteristics of the pig gut that are similar. There are characteristics of the ferret gut that are also--there is no perfect model but there are more and less perfect. The pig is closer than the mouse but it is a lot more expensive.

DR. BENEDICT: So back on schedule; Dr. Clydesdale.

DR. CLYDESDALE: I think the first thing to look at would be the 95th percentile users, and we can get that from data, not only of yogurt but other fermented products and cheeses and find out what 95th percentile users are consuming.

We haven't had any problems, so it will give you an idea of extreme upper levels that don't cause a problem. I think that that would be a good place to start so we are not looking at stuff that is lower than that.

DR. BENEDICT: Dr. Hotchkiss?

DR. HOTCHKISS: The answer to that question also depends, in part, on whether you are talking about a concentrated supplement-type formula or you are talking about foods. Exposure in foods is also often self-limiting and, in some ways, makes food a better vehicle for that reason.

If you are talking about a lyophilized culture, you might be talking about a completely different level of exposure.

DR. BENEDICT: Dr. Clemens?

DR. CLEMENS: I appreciate that comment by Dr. Hotchkiss. I fact, all the pediatric studies with which I have been involved in the United States and Europe, in fact, that has been self-limiting. You would have to consume orders of magnitude more formula than you could possibly

consume to get a potential overdose, and an overdose has never been experienced in any of these kinds of studies.

DR. BENEDICT: Of course, we have dealt, in the past, with things like teas where people have concluded that a little is good and more is better, and it has been very deleterious. I think, perhaps, one of the things that we might want to address is, in addition to the very solid thousands of years about many of the things, the exceptions will be the ones that will cause the most trouble, the kind where you take a capsule and if you are supposed to take one three times a day, and three times a day is more appealing to you.

What are the parameters for establishing a safe exposure level for something like that when--certainly, there are animal models but the final arbiter is going to be the human. How do we do that?

Dr. Fukagawa?

DR. FUKAGAWA: This is somewhat of a digression, but I think it would be exciting to have an RFA out, not necessarily from the FDA but, perhaps, other agencies because when we talk about this broad sense of feeling better, there may be true scientific reasons why one would feel better; namely, peptides that are released that might bind to receptors in certain parts of our brain that will end up increasing our euphoria.

I realize that nicotine is something that we are not necessarily promoting, but, certainly, that is an ingredient that people use because it does help to make them better or, in cases of ADD, might help them focus and work. So I think if we can begin to look at modes of action or mechanisms of action with these probiotics, looking at-- being able to support research along those lines would be rather exciting.

I would think industry would love to partner with scientists along those lines. So it is a digression.

DR. BENEDICT: But a fine one. Any time you want to discuss more money for science, it is a welcome topic.

DR. FUKAGAWA: Thank you. I thought I should throw that in.

DR. BENEDICT: Dr. Buchanan?

DR. BUCHANAN: I just get nervous. They keep looking at me when they do that.

DR. BENEDICT: Yes ; of course.

Dr. Clydesdale?

DR. CLYDESDALE: I think establishing some of the animal models, as Dr. Russell mentioned, and establishing no-effect levels in these and then, after you establish the no-effect levels, decide what kind of safety factor you want depending on its mode of action. Then you can do a multiple of that no-effect level for use in humans.

DR. BENEDICT: Thank you. I see a frown. Dr. Yetley?

DR. YETLEY: I was just going to ask Fergie, do you think that that model works for something that you want to be active? That is the classic tox model, you find the no-effect level. But do you also, then, add in an-effect level?

DR. CLYDESDALE: I guess, Beth, I am not worried too much about the activity, the bioactive part of it, since we are told that most of them die anyway. I am worried about getting a real load of whatever the bacteria contains inside itself in the bacterial cell walls, particularly if you take them as supplements.

If this is really overdosed, maybe there is a no-effect level from that--of any kind of effect. I am not talking about something that is going to kill the animal, but I am talking about functional effects that could be deleterious rather than functional effects that could be helpful.

DR. BENEDICT: Any additional thoughts? Okay; the final question. What do you consider appropriate criteria or parameters for evaluating efficacy? The question is to define efficacy, and I think that is a good place to start. We could start with that. Efficacy, at face value, seems straightforward. You say it does something and it does it.

3ut the real mine field there is what you say that it does.

Dr. Clydesdale?

DR. CLYDESDALE: The Canadian government did a survey of things whether they should use them in conducting physicals or not. They defined efficacy as--they defined effectiveness, which is more than efficacy, as efficacy times compliance, which was an interesting idea.

DR. BENEDICT: Interesting.

DR. CLYDESDALE: So if someone is saying, "Eat this food," or, "Take this supplement," how long do they have to take it? Do they have to take it every day? Do they have to take it twice a day? What if they just eat for two days; does it have any effect?

DR. BENEDICT: Dr. Hotchkiss?

DR. HOTCHKISS: It seems to me, in this context, you have to define efficacy in terms of what is claimed about it, to what extent does a product, whatever that product may be, meet, in a scientific way, the claim?

DR. BENEDICT: And we return, then, to "it makes me feel better." How do you evaluate that?

Dr. Hotchkiss?

DR. HOTCHKISS: An obviously very nebulous claim but, nonetheless, if that is the claim you want to make, then you should provide scientific evidence to support that. If the claim is so nebulous that you can't support it, then

you don't get the claim. I guess that is what I am saying.

So if you make claims that don't make any sense, then you can't support claims that don't make any sense and you don't get that claim.

DR. BENEDICT: Dr. Clydesdale?

DR. CLYDESDALE: There are psychological techniques in scaling to do such things as measuring how hungry you feel. So I am certain that there are psychological techniques in scaling to say, "How do you feel, in general?" If you want to run those under some kind of controlled testing, I think you could come up with answers on that.

DR. BENEDICT: So even in the context of the 45 percent that we heard a few years ago who feel that they have intestinal discomfort, if you reduced that--

DR. CLYDESDALE: I wasn't even talking about intestinal discomfort. You just said, "I feel better."

DR. BENEDICT: Okay; gotcha. Dr. Clemens?

DR. CLEMENS: Dr. Clydesdale, how would you want to apply that scale to a pediatric population?

DR. SIGMAN-GRANT: Parents. Parental.

DR. CLYDESDALE: I don't know. How much do they cry?

DR. BENEDICT: Dr. Sigman-Grant?

DR. SIGMAN-GRANT: There are lots of techniques in

the social sciences to measure perception. For pediatric, you can measure the parental perception. And they are good predictors of at least how they perceive their baby to be reacting.

So you could set up, and there are actually very detailed methods on how to make those measures valid, reliable, repeatable, consistent. But you are talking about another RFA. But they are available. And they are scientific. But they are not in the quantify-type that we measure.

DR. BENEDICT: Dr. Montville?

DR. MONTVILLE: The gold standard, of course, the double-blind, placebo-controlled, clinical study. Is that what we want, no matter how you measure it, or is something less than that okay?

DR. BUCHANAN: While you are thinking about that question, also reflect on everything that you have indicated so far in responding to this question have been trials in humans. So are you also implying that everything should be done in humans?

DR. BENEDICT: Exactly. It is a lot cheaper to do it in the test tube. We are talking about small companies. We are talking about people who may bring a single product to market and, perhaps, not have the financial backing to do humans. Do we need to ask for another RFA for development

of animal models or even organ-culture models for this kind of thing?

Dr. Fukagawa?

DR. FUKAGAWA: But we did agree that this would likely be claim-specific, in which case, I think we go back to the fact that it would be in the human, since many of the claims are for effects in the human.

But I think the broad-based example that you used of "Do you feel better?" is something that we did not think, I thought, would be something that we would entertain because, unless there is a specific effect, and more defined effect, as Dr. Russell had said, then it would be very hard to substantiate.

DR. BENEDICT: Dr. Hotchkiss?

DR. HOTCHKISS: I appreciated Dr. Russell's comment, particularly about the ferret, having worked a lot with GI studies in the ferret. I can tell you that, generally, the people I ask agree that the ferret is good, but the ferret is still a very difficult model and can be shot down as a perfect model or even near-perfect model for the human situation.

So if you are making human GI-tract claims of whether it is specific or broad, from my experience, it is just not currently possible to have an animal model that you can automatically extend to the human situation.

DR. BENEDICT: Dr. Sanders?

DR. SANDERS: Going back to thinking about this in terms of probiotic-specific issues, are double-blind human clinical trials or volunteer studies required for a structure/function claim in non-probiotic foods? Is there an FDA approach, for example, that if someone says "enhances immune function" on echinaceae, is a double-blind, placebo-controlled study considered to be the standard that has to be met to make that statement?

DR. YETLEY: As I indicated earlier, we don't have formal standards. It would have to be adequately substantiated.

DR. SANDERS: But exactly what that means is not really defined?

DR. YETLEY: It is not defined. Now, in terms of health claims, there is a requirement that there be human data that adequately substantiates--

DR. SANDERS: For the health benefit in terms of the structure/function. I guess what I would offer is relative to our discussion on probiotics, that the standard should be equivalent. A structure/function statement made on a food or a supplement in a particular target area should have to meet the same criteria.

I don't see anything in probiotics that would specially would change that. What I do sense, or get a

sense of in terms of my evaluation of probiotic literature, is that there is not good scientific consensus, and this gets back to Dr. Clydesdale's original point a long time ago. In terms of what is the validity, a measurement of validity, for those studies and is there an animal model for immune-system function that gives some degree of scientific--that people can develop a scientific consensus on, or not.

Again, that is a broader question beyond the area of probiotics. In my opinion, that is an area that needs a huge amount of work, is the development of a scientific consensus on what models are meaningful for people for a variety of these areas, including GI-tract health.

I am not willing to abandon that. I think that there can be some definition of that area as well.

DR. BENEDICT: Dr. Sigman-Grant?

DR. SIGMAN-GRANT: I was just wondering about adding something to infant formula. There is an Infant Formula Act which has specific ingredients, if you would. Would adding probiotics conflict with that Infant Formula Act? That may be one subpopulation and one particular food for which you need very definitive double-blind clinical trials.

DR. YETLEY: An infant formula containing a probiotic would have to meet all the usual requirements. It would have to have food-additive or GRAS status for that

intended use and it would have to follow the 90-day notification of intent to market a new infant formula.

That requires documentation of--

DR. SIGMAN-GRANT: Fairly good documentation.

DR. YETLEY: Documentation that it supports healthy growth.

DR. SIGMAN-GRANT: What about the microbiological part of that, that second part, besides just ingredients. Aren't there some standards on microbiology?

DR. YETLEY: There are food standards that formulas would need to meet relative to--

DR. SIGMAN-GRANT: Do those have to be changed if you are adding--

DR. YETLEY: It is an issue. We did propose GMPs for infant formula with a tolerance--I am not sure that is quite the correct term, but there was an indication of a maximum level of organisms, microorganisms, in the formula. The issue did come up in comments as to whether or not--or how would that apply of probiotics were to be added.

DR. SIGMAN-GRANT: Yes; because those were for pathogenic organisms.

DR. YETLEY: It is not an issue we have resolved, but it has been raised.

DR. BENEDICT: I would like to ask a question of Dr. Russell and all the microbiologists over there. When

one says that the pig is a good model, does that mean its immune system looks okay? Does that mean its gastrointestinal flora models that of humans because it eats almost anything like we do?

What are the criteria that are applied to say that the pig is a good model compared with ferrets or anything else, mice? How do we know it is a good model and, if it is a good model, can we take a piece of pig intestine and deal with it in vitro? Do we have to do it in vivo?

I am just trying to find a way that people can ask these questions without going all the way to humans first. So, does anyone have a comment on that?

Dr. Buchanan does.

DR. BUCHANAN: Traditionally, the pig has been looked at as a model for intestinal infectious diseases in that it, one, demonstrates symptomatology that is similar for similar biological agents. So, for example, anerotoxogenic E. coli was originally a veterinary problem. It turned out that there were different strains associated with pigs and humans but the disease, the disease mechanism, the response to the organism was very similar in both of those.

And there are a series of other intestinal infectious agents, at least of a bacterial origin, that have a very similar mechanism of pathogenicity. That is where I

think a lot of the model is associated with it.

As an omnivore, I think it has a lot of the characteristics that we see in humans also in terms of intestinal physiology, but I will rely on our experts there to put more in. But I think it more closely models the anatomy of the human even, in some cases, what we would consider a closer relative.

DR. RUSSELL: That is my understanding of it, too. I have never worked with pigs. I have worked with ferrets. The ferrets have peculiar similarities, too, to the human with regard to anatomy but, also, they have Helicobacter infection and a chronic gastritis which makes it, for certain issues and certain problems, perhaps a Helicobacter problem, to be an appropriate model.

Also, these animals absorb, which we are interested in, carotinoids, which most other animals do not. The rat does not, particularly. The pig does not. The guinea pig does not. The mouse does not. The rabbit does not. But the ferret does. They are carnivores, so they are not similar in bacterial populations.

DR. BENEDICT: Dr. Fukagawa?

DR. FUKAGAWA: This was raised by someone in the audience. Is there anything we can learn from the animal sort of literature, I mean animal production, animal health?

DR. BENEDICT: USDA, you mean?

DR. FUKAGAWA: I guess it would be USDA; is that right? Use of probiotics to stimulate animal health.

DR. BENEDICT: Dr. Buchanan has a comment for that.

DR. BUCHANAN: Yes ; there is an extensive literature on the use of probiotics. Now, a lot of the research in probiotics in relation to food safety has been associated with competitive exclusion and keeping unwanted bacterial species out of farm animals. So, for example, feeding of either a defined or undefined E. coli culture to chicks during the first day greatly suppresses the incidence of Salmonella. That has been a very successful application of this technology.

There has also been a great deal of probiotic work that has been focused on the efficiency of the rumen. I know of less that has been directed specifically to the large intestine but that would probably be in association with the feeding of horses who are cecal fermenters. so you might have some literature there.

But there is an extensive literature on the use of probiotics and it is an active industry now. So I am sure there are some lessons.

DR. BENEDICT: Within that context, it is probably appropriate to say, I suppose, that if there is another meeting, perhaps investigation of the accomplishments of the

Japanese in these areas might be good. We were presented with a portion today written by Dr. Sanders, I think, of an article. Perhaps, we could investigate further that for the next meeting that you guys have.

Are there additional comments on efficacy, criteria for evaluating efficacy? Or are there additional questions from FDA that we have not addressed fully or at all thus far?

Okay. Then, perhaps, what we can do is ask the members of the advisory committee if there is anything that you would like to say to help FDA, that we haven't said, any guidance you want to give before we go that might be helpful over the next weeks or months, that we haven't mentioned or that you would just like to refocus? Things you would like to have because you are going to have to contemplate this again?

Dr. Russell?

DR. RUSSELL: Is there a framework being worked on to try to get a better definition of what adequate substantiation means for structure/function claims in general? In other words, that is also so kind of loose and vague that it is hard to know what adequate substantiation means unless you better define it.

It came up here with probiotics, but it is the same problem for botanicals and so forth in general.

DR. YETLEY: It certainly has been discussed a lot. I am not directly involved in it anymore, so I can't answer your question exactly. But it is certainly something that we have discussed a lot and we have discussed with other expert groups. I don't know where the process is.

DR. RUSSELL: But the agency is eventually working toward a better definition of that?

DR. YETLEY: We are certainly giving it a lot of thought.

DR. RUSSELL: Giving it a lot of thought; okay.

DR. BENEDICT: Dr. Clydesdale?

DR. CLYDESDALE: We had a meeting, the National Academy of the Food Forum, yesterday and spent a lot of time discussing that and came to about as firm conclusions as we have come to today.

DR. BENEDICT: It is a consistent malady.

Dr. Hotchkiss?

DR. HOTCHKISS: Just to reemphasize the point you have made. It certainly would, I think, help my own thinking about this if someone who has been involved in this issue, either in Europe or Japan, were to come before us and present the evidence or, perhaps, lack of evidence, whichever way it is, because there is, particularly in Japan, as was pointed out, a very long history of this consumption or the fact that a large number of people

believe this is helping them is different than does it really.

I just wonder what the evidence really is that it does some good or doesn't do some good. It would be nice to hear from someone who has rigorously looked at that.

DR. BENEDICT: One last chance to have all your thoughts recorded for posterity, all your questions asked. Seeing none, I guess we stand adjourned. Thank you all for your participation. Thank you for your great comments. I am sure it has been very helpful.

[Whereupon, at 12:45 p.m., the meeting was adjourned.]

C E R T I F I C A T E

I, ALICE TOIGO, the Official Court Reporter for Miller Reporting Company, Inc., hereby certify that I recorded the foregoing proceedings; that the proceedings have been reduced to typewriting by me, or under my direction and that the foregoing transcript is a correct and accurate record of the proceedings to the best of my knowledge, ability and belief.

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