TRANSCRIPT OF PROCEEDINGS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

FOOD ADVISORY COMMITTEE MEETING ON PROBIOTICS

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

FOOD ADVISORY COMMITTEE MEETING ON PROBIOTICS

Wednesday, September 27, 2000

8:30 a.m.

Hilton Towers-Gallery I and II
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MILLER REPORTING COMPANY, INC.
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H. Rex Gaskins, Ph.D.

Daniel J. O'Sullivan, Ph.D.

Mary Ellen Sanders, Ph.D.

R. Doug Wagner, Ph.D.

FDA

Dr. Robert Buchanan

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C O N T E N T S

	Pase No.
Introductions and Overview	4
Presentation of Questions and Discussion	9

P R O C E E D I N G S

Introductions and Overview

DR. BENEDICT: Good morning. Welcome to the Food Advisory Committee meeting of the Center for Food Safety and Applied Nutrition, Food and Drug Administration, second day. The topic of our discussion for yesterday and today is probiotics.

Before we begin, I think we should compliment and thank FDA for its selection of some outstanding speakers. We heard a wonderful program yesterday, very succinctly presented. We are grateful for the information and those speakers have joined us at the table today, so that during what is essentially a roundtable discussion, they will be available as resources for members of the committee as we begin to provide advice to FDA on this topic.

Before we go too much farther, I think it is probably appropriate if we all just introduce ourselves so that the folks making the recording and the folks listening at home will know where we are all sitting.

My name is Steve Benedict. I am from the University of Kansas and I am an immunologist.

MS. DeROEVER: Cathy DeRoever, Center for Food Safety and Applied Nutrition at FDA. I am the Exec Sec for the Food Advisory Committee.

MS. HAYDEN: Linda Hayden, Office of Science with

CFSAN.

DR. HOTCHKISS: Joe Hotchkiss, Cornell University, Department of Food Science.

MS. RICHARDSON: Donna Richardson, Howard University.

DR. MONTVILLE: Tom Montville, Professor of Food Science, Rutgers University.

DR. FUKAGAWA: Naomi Fukagawa, University of Vermont, who started out as a pediatrician and now does gerontology.

DR. O'SULLIVAN: Dan O'Sullivan, University of Minnesota, Department of Food Science and Nutrition.

DR. WAGNER: Doug Wagner, microbiologist at the FDA's National Center for Toxicological Research.

DR. BUCHANAN: Bob Buchanan, FDA, Center for Food Safety and Applied Nutrition, Senior Science Adviser, and Director of the Office of Science.

DR. SANDERS: Mary Ellen Sanders. I am a consultant with Dairy and Food Culture Technologies.

DR. CLEMENS: Roger Clemens, Professor of Food Science and Nutrition, Cal Poly Pomona and freelance consultant.

DR. GASKINS: Rex Gaskins, University of Illinois.

DR. CLYDESDALE: Fergus Clydesdale, University of Massachusetts at Amherst.

DR. VILLARREAL: Roberto Villarreal, University of Texas, San Antonio.

DR. COHEN: Mitch Cohen, Division of Bacterial and Mycotic Diseases at the Centers for Disease Control.

DR. RUSSELL: Rob Russell, gastroenterologist and nutrition from Tufts and USDA.

DR. SIGMAN-GRANT: Madeleine Sigman-Grant, University of Nevada, Reno, Cooperative Extension.

DR. BENEDICT: Thank you.

So, what we hope to do today is provide advice to FDA. Before we do that, we might ask Ms. DeRoever if she has any beginning advice for us. None taken.

So, just a brief recap before we actually get into the business of the day. So, yesterday, we heard some fine presentations about probiotics themselves, about what is available in the marketplace, and some thoughts about what might be coming on line.

We heard about the organisms themselves, we heard about the fact that it is a huge ecosystem, methods of analysis. We talked about the immune system and the immune response. We talked about infant foods and formula.

One of the sort of dichotomies would seem--and this is personal opinion gleaned from the fine talks that I heard--is that we are dealing with a huge ecosystem of which we can recognize about 400 organisms with an additional 400

to 500 that we can't recognize and don't know--we know they exist, but we don't know what they are, and in some ways it seems difficult to effect a lasting change in the system. However, pathogens can certainly effect dramatic, sometimes apocalyptic changes.

Yet, the time to recovery varies depending on what happens to the system, and so as we consider these things, I think it is important to think about the big picture and the massive number of people who are affected by greater or lesser insults to the system and do fine, and the possibility of getting a lasting change when you notice that 14 days later you can't find the organism you put in.

I think all of these things we have to consider if you don't mind.

So, today, what we are asked to do is focus on a scientific framework for what FDA should do next in addressing the question, the emerging question of probiotics, and it would be good if we used the same format as yesterday.

The important thing we must do is provide a cogent transcript that can be poured over later by folks who will actually deal with policy. So, again--and I am probably the worst person at this--it would be nice to avoid a free-wheeling discussion where we all just jump in with our many opinions because people won't be able to keep track.

Sadly, I will ask that we do the same thing we did yesterday, which is get the attention of Ms. DeRoever and we will take everyone's comments in the order that she writes down your name. This will allow us perhaps less spontaneity, but I think it will be much more polite and straightforward.

If I forget to mention your name when you begin to speak, please don't hesitate to do that, so that the folks can write down exactly who you are and, as Ed Brandt likes to say, the Master's degree students who are studying your comments in five years will be able to know that you actually made them.

So, as I said, what we want to do is establish a framework, a scientific framework by which FDA can then launch its next group of activities with respect to probiotics.

We are going to talk about safety assessments and efficacy assessments today, and we want to keep in mind how many of these things affect the general population and how they affect specific subpopulations of individuals that might be called upon to interact with probiotics.

As we go through the specific subsets that we are asked to discuss, once we have discussed things sufficiently, a subjective opinion, of course, we will then be asked to put things into priorities, so that FDA can read

through this and say, well, the first thing we need to work on is this, and this might be extremely minor, but we might want to think about it in the year 2020.

Also, be aware that FDA will probably return to the Food Advisory Committee for additional fine-tuning of this. With that in mind, we don't really have to draw conclusions today as much as we have to get as many ideas on the board as possible with priorities, so FDA can come back to us and say, "Did you really mean this?" No. So, FDA can have plenty of things to work with.

Presentation of Questions and Discussion

DR. BENEDICT: So, if you have the piece of paper that details the questions, the committee questions that we are going to get to, the first one listed is safety considerations, and there are several subsets of this.

So, this question involves the following things. I will sort of read it to you.

What FDA has asked is: Given changes in scientific nomenclature, what terms could be better articulated, defined or clarified to advance mutual understanding about these products?

So, that is what FDA has asked. What I would like for us also to consider, if FDA is called upon to define a number of things, including probiotics, what are the essential components of any definition of any term that we

propose today that needs to be defined.

We don't have to write the definition, that is not our job, but the things that we think should be included or excluded should come out on the table.

Also, recall that whatever goes into a definition will in part, I think, govern how some substances are regulated, so we want to be sure we just say things, and other folks will deal with that.

A final thing to consider in terms of nomenclature is can we use specific terminology--and we may not be able to--but can we use specific terminology to link groups or organisms with the putative physiological effects that they might have, or putative sites of delivery, as we learned a little about yesterday.

So, the first thing that I think we should consider is terms and definitions, and perhaps to focus our thinking or maybe to save time, I spent some time last night gleaning phrases from the various definitions and from conversations and questions in some of the presentations, and what I would like to do, and if you have an interest you can take out your crayons and write down things that strike you as positive or negative, and if you don't, that's fine, too. I have a few things.

I will just read them out to refresh your memory about what we heard yesterday, and then we can perhaps

address the specifics.

So, basic terms that we have heard, probiotics, of course, prebiotics, symbiotics, and then a definition of anything will include organism, or it might include viable organism, or it might include carefully defined strains of organisms.

I also might, as we heard, we might deal with substances produced by an organism, and one assumes that these would be in vivo after application, not just produced in vitro, and that become a different subset.

We need to think about single versus mixed culture, and then terms, active terms, modulate the growth of other organisms was listed, also modulate the development of the immune system was one of the activities that we heard. In many of the definitions include have a beneficial affect on. This could be the intestinal microbial balance. It could be the immune response, either mucosal or systemic, and just pause for a minute.

There is a term. The phrase is "dietary adjuvant." To an immunologist, of course, adjuvant means one thing, but the word adjuvant comes from the Latin adjuvare meaning to help, and so a dietary adjuvant could be something that helps the diet, and I wasn't clear about which meaning this was. So, if we choose to use adjuvant, we may wish to define it a little better.

Other terms are beyond basic nutrition for the help that is given. Improving nutritional and microbial balance, interacting with the host mucosa, a touchy one - clinically validated health effect, ingested in adequate amounts. Some folks were mentioning that.

Now, another thing to consider is, as we learned yesterday, looking down the road all of these things may not be ingested. We learned about vaginal effects, wound healing effects, and so topical applications are something that either may exclude ingested from a definition or may need to be included.

One could envision suppositories to get to the intestinal tract, because we need to target different--as we heard, there are different places that need to be targeted.

The other question is: Is the mucosa always the target? Well, we heard that wound healing might be in the offing, and so there you have it.

So, those are the terms that I was able to come up with that occupy the thoughts of people. If anyone has additional terms that they would like to add to this list, please do so at this time, and then we can start after that a discussion of what we think should really be important.

May I ask one other thing. If you could all turn your name tags somewhat obliquely, so that I can see your name, even though I may know you well, I, in the heat of

battle, sometimes forget, and I wish to make no error.

Do people have additions to this list of terms? Dr. Montville.

DR. MONTVILLE: Steve, I don't know quite where this fits in, but the definition of the organism, the characterization of the organism, and exactly what it is we are talking about, and how we can prove that it is the same one in five years as was approved today.

DR. BENEDICT: That's good. So, carefully define strains over the long term.

Dr. Russell.

DR. RUSSELL: Another word that I think was used differently by different people was colonization versus prolonged residence time, and I think we need to be clear on what we are talking about.

DR. BENEDICT: Yes.

Dr. Clemens.

DR. CLEMENS: You might want to consider just lactic acid bacteria, for example, because many organisms were discussed yesterday that may not be specific to lactic acid bacteria, but lactic acid bacteria are currently used in the binder as comparable with lactic acid bacteria.

DR. BENEDICT: Yes, Dr. Sigman-Grant.

DR. SIGMAN-GRANT: I don't know if this fits in your list of terms, but there seemed to me a lack of clarity

between prevention or promotion of health, treatment of disease, and in terms of what they are used for, and I just think that needs to be defined somewhere, and if not in this set, then somewhere down the road.

DR. BENEDICT: Thank you.

All right. So, now the hard part is figuring out important it is to include different things. To me, a description of the organism or organisms used, so a definition might say mixed or purified or extremely characterized or whatever, organisms that you do other stuff sith.

so, what do people feel about how the organism should be addressed in a definition? The committee, do you think it is important to define specifically the organism that goes in? And all the organisms that go in, as in the case of yogurt, for example, how specific do we want to be or do we want the FDA to be?

Let me just say before I go further, anyone who actually know what I should be talking about, mostly Dr. Buchanan, if I start getting us off track and wandering around, just kind of let me know that you don't care about this, you guys.

DR. BUCHANAN: Just a brief comment. We can provide you with the best estimate of the definitions between drugs, dietary supplements, and foods that we can

based on our legal requirements.

I would, in terms of priorities, suggest that the committee focus on dietary supplement uses and food uses, that therapeutic uses for the treatment of disease would be classified as a drug, and that would be the purview of a different advisory committee.

So, as you are thinking about future applications, please focus on dietary supplements and foods. Now, if we need to get a better legal definition about what a drug is, and it's a hazy definition at best, but think about the treatment of symptoms. If you are giving something to treat a disease state, assume that that is a drug, and that is not the purview that we are dealing with here when we are asking for advice.

Also, please, while the applications may be useful, let's try and focus on the actual ingestion of the viable organisms, not topical treatments, not vaginal treatments. Those would be more directed probably towards a drug application.

DR. BENEDICT: Thank you.

Dr. O'Sullivan.

DR. O'SULLIVAN: Based on where probiotics and the organisms are at present, it appears that the term probiotics might be beginning to get too broad, and possibly needs to be subdefined like, for example, we hear about some

beneficial effects that occur which is not specific to any one organism, just any lactic acid bacteria which can essentially get into the target sites and be tested at high numbers, and then there strain-specific effects.

So, possibly there is a general and a specific definition rather than trying to bundle everything into the one word, it might get very cumbersome.

DR. BENEDICT: Dr. Sanders.

DR. SANDERS: Just for clarification for me, I can understand the importance of this group's focus on foods and dietary supplements, as Dr. Buchanan pointed out, but in terms of definition of the term probiotic, if it is going to be used in a drug application ultimately, I am wondering if it makes sense for us to consider the term probiotic, so that if, in fact., there becomes a legal definition of this, it doesn't have to be defined two different things for two different applications, which then could ultimately be confusing or whatever, that perhaps the definition portion of the efforts of this committee need to consider ultimate. drug applications. I don't know.

DR. BENEDICT: Thank you.

MS. DeROEVER: This committee would not be asked to consider any drug or medical device unless we actually had a joint meeting with one of our sister centers. I really think we are best focused on the food uses for the

purview of what we are doing.

It is also in the interest of time, and I think it has been mentioned perhaps once or twice before this may just be an initial meeting. If we have comments, certainly they will be in the record, and we can take them to a sister center and internally decide what approach to take based on those comments.

DR. BENEDICT: Dr. Hotchkiss.

DR. HOTCHKISS: As was pointed out I thought very clearly yesterday, there are a variety of definitions of probiotics both from a scientific perspective, but even broader definitions in the regulated industry, and I think FDA's first priority should be to clarify its position on that definition. That would help FDA, as well as the regulated industry because that would help them decide which directions they wanted to go with their products.

The second most important definition is, in my view, organism, strain, and so forth, and as we saw, the taxonomy, because of introduction of modern methods for dong taxonomy is changing and likely to continue to change, therefore, you have to worry about making the normal kind of definitions that you do, so it seems to me FDA has to consider including perhaps things like genetic or biochemical requirements within that definition. If the taxonomy does change--which it is very possible it will--

that the organism does not in a particular application, particularly a food or supplement application, so I think those two definitions are really first based to get on with the process, and in my belief in having interacted with some of the industry on this issue, making those definitions would help move the industry forward because they would know what the rules of the game are going to be.

[Pause.]

DR. BENEDICT: This is not lively enough.

Dr. Cohen.

DR. COHEN: Would there be some advantage in trying to look at the issues of food and dietary supplements separately?

DR. BENEDICT: Dr. Hotchkiss.

DR. HOTCHKISS: Perhaps, but my understanding of the way food and dietary supplement and structure function claims, and so forth, are going to work out, that that differentiation between those two terms is going to be less based on the product than it is based on the claims on the product, and so forth, and the claims are brought forth, not by FDA, but by someone wanting to make that product or use that product, and that seems to be very hard for us, you know, given the yogurt or whatever to understand which category that falls into.

DR. BENEDICT: Dr. Montville.

DR. MONTVILLE: I think you are both right in that if we look at foods, it would seem that the only requirement is safety, so we could start with safety. Then, when you go to nutritional supplements, we are talking about safety and efficacy, that they do something.

DR. BENEDICT: Dr. Buchanan.

DR. BUCHANAN: Just to again provide a little guidance to keep this on focus. While there are differences in the legal system, in the law associated with dietary supplements and foods, the issues that you should be facing are, are there scientifically based differences between what would have to be considered with a dietary supplement versus what would have to be considered by a food.

So, for example, in your definition, your consideration, would be the fact that you have concentrated a culture into a capsule have some special attribute scientifically versus if you just took the product and fed it as part of a good.

So, I think those are the kinds of things that you should be considering, but I would not worry too much about segregating what is the definition of a dietary supplement versus a food in the legal definitions. Leave that to our legal staff. They get paid a lot of money to do that.

DR. BENEDICT: Dr. Clydesdale.

DR. CLYDESDALE: Just to continue on Dr.

Buchanan's comments, I think it would be very important in the definition because we think of probiotics and food, we are really thinking of a substrate which, by and large, controls the type of probiotic that's in there very much so, the type of organism that is going to grow is going to depend upon the conditions that the food imposes on those organisms, whereas, when we get to dietary supplements, we are going to have to be sure that we know exactly what's there and the amount that's there, and we can tell the consumers what they are getting.

So, not only do we have to worry about concentration effects, but we have to worry about what is there, because there is no exterior control once you separate these things on what will grow or what won't grow or what might be there, whereas, the food does confer some exterior or external control on what grows.

DR. BENEDICT: Dr. Cohen. Pass.

Dr. Fukagawa.

DR. FUKAGAWA: Yes. Could you please clarify for me again. Our charge is really to define and assess or come to some kind of opinion with respect to the use of these organisms in food components when a health claim is associated with it, correct? Or is it, for example, it is labeled on yogurt that it contains--that is not something that we now need to address because yogurt has been on the

market for years. If you could just clarify that for me.

DR. BENEDICT: I will defer to Dr. Buchanan, who I am sure can do a much better job.

DR. BUCHANAN: What would be very helpful--and Let's just pick a single example here. We have the term probiotic, what we are going to hear about. In the definitions that we heard presented yesterday, and discussed around the table, there were a variety of factors that were or were not included in different definitions.

Some of the definitions said that you had to have viable organisms. Other definitions said that you did not have to have viable organisms. Some said you had to have intact organisms. Some said it could be products of those organisms. Some said that it had to be lactic acid bacteria, others used a much broader range in the definition.

Do they have to be viable, nonviable? Do they have to have a beneficial effect or not a beneficial effect? Then, of course, you get into what is a beneficial effect, which is another definition.

But if you think back to the different definitions that were put up on the board, and there were different terms used to describe the criterias within those, which of those criterias are important for us to include in a definition that we will have to develop for a probiotic, and

what kind of priority should we be considering those.

DR. BENEDICT: Dr. Hotchkiss.

DR. HOTCHKISS: Let me throw something out on the table to try to get us moving on this. I would suggest that the term probiotic, as most commonly used, would have to be something containing viable organisms.

There was some discussion of that yesterday, but I think as most commonly used, it is a viable, that is, capable of reproduction, that it must be ingested--at least in the context of this committee--that it must be ingested, that there must be a demonstratable positive health benefit to consumption or ingestion of this organism.

I think some of those kinds of components of a definition cover both the supplement and the food category, but I think that we should really try to narrow this down as commonly used. As I said, viability is a key, known organism, I think is a key to a definition, and maybe some others will come to mind.

DR. BENEDICT: Okay. Let's deal with that. How many of the folks on the committee think the organism should be viable? Let's just go with do we agree that the organism in a probiotic should be a viable organism.

Let's do a show of hands and then we can count, and that will happen.

Those who think the organism should be viable, who

are on the committee, raise your hands. This will be the committee.

[Show of hands.]

DR. BENEDICT: The score is 8.

Those who do not think viability is a factor, please signify, and abstention.

Eight in favor and one abstention.

Dr. Fukagawa, please.

DR. FUKAGAWA: I just wanted to clarify that I think my vote is based on the fact that I don't think we have good scientific data to be able to assess the issue of components of a nonviable organism, or at least I haven't felt that the discussion was compelling, providing support at the other side, so I would go with Dr. Hotchkiss' recommendation that we consider the viability.

DR. BENEDICT: Dr. Hotchkiss.

DR. HOTCHKISS: One of the reasons for viability is if you inc1ude products of organisms that are no longer viable, you really have included a whole host of things that are including things like vitamins, and so forth, that are produced by fermentation. You have really opened up in a different direction that would not be considered under the rubric of probiotic in my view.

DR. BENEDICT Dr. Clemens.

DR. CLEMENS: Thank you, Joe, for your comments.

I assume on viability you include that the organisms can be resuscitated.

DR. HOTCHKISS: Certainly.

DR. BENEDICT: So, the next word in Dr. Hotchkiss' panoply of terms is ingested, and since this is the Food Advisory Committee, for our terms, ingested is crucial, as was pointed out by Dr. Buchanan.

We will leave to the FDA the decision of whether they want to make, as has been suggested, a generalized definition that affects anything that is probiotic.

Dr. Buchanan.

DR. BUCHANAN: Certainly we heard--I will take it as a recommendation--that in whatever definition we come up with for probiotics, that we try to harmonize that with our sister centers associated with drugs.

DR. BENEDICT: Thank you.

So, what about a demonstrable benefit? Are there comments on whether a probiotic should show a demonstrable benefit? In the word "demonstrable," of course, we will need a definition.

Dr. Russell.

DR. RUSSELL: Once again, I am going to have problems when we talk about benefits of bacterial balance. Those terms are so vague and meaningless, and we don't know that they really have any health benefit or not. The fact

that you are putting more bifidobacteria into colon, so young children may or may not have a health benefit, and we don't know that more or less clostridia in the adult colon, or more or less bacteroides makes them any less healthy.

So, to change that by increasing a certain organism, I am not sure, unless we can show that that organism prevents diarrhea or some disease, it is going to be hard to define what health benefit means. I just bring that up.

I know you can't just say has an effect probably because you don't want it to imply that probiotic would have a negative effect, but I just worry about health benefit.

DR. BENEDICT: Dr. Hotchkiss.

DR. HOTCHKISS: I certainly agree with Dr. Russell. In my view, simply changing the microbial ecology of the lower GI tract does not in itself constitute a health benefit. On the other hand, as we heard some evidence, some very good evidence I thought yesterday, there are more direct or potentially more direct health benefits from probiotics for which FDA has a responsibility to bring forth if they can be demonstrated. So, FDA, as part of the Public Health Service, has a responsibility, not only to prevent unsafe things, but also to bring forth or allow things that produce positive health benefits, not changing the microbial ecology of the gut or whatever per se, but a demonstratable

in an accepted medical kind of test or trial, in my view.

DR. BENEDICT: So, let me just interject. Then, that would mean that just synthesizing the two, on the one case a probiotic would include a globe number of things, and in another case we would ask if it is going to be called a probiotic, that it have a benefit.

That is probably enough for FDA to deal with.

Dr. Montville.

DR. MONTVILLE: I was wondering if we couldn't kind of parse this out into a general health benefit in the definition and then deal with what exactly is a health benefit in the claim because we heard that there are clinically proven, there are generally thought to be, there are anecdotal, and there could be a whole spectrum of claims ranging from, you know, is thought to, to improves or to--is clinically proven to, and then parse that all out and what claims would be allowed, and what you would have to do to prove the claim.

DR. BENEDICT: Dr. Sanders.

DR. SANDERS: I feel very strongly that the concept of consumption for health benefit has to be part of this definition, because that is just at the heart of the concept of what a probiotic is, and I don't know if it is possible within the definition to differentiate defined health benefit with intent.

In other words, a definition that says a probiotic is added or consumed for a health benefit, you know, states that the intent is that that is there, and then it is up then to further definition or how the product ultimately is regulated to define exactly what degree of evidence is required to substantiate that type of a statement.

DR. BENEDICT: Dr. Clydesdale.

DR. CLYDESDALE: I' would-agree with Dr. Russell. I have a great deal of difficulty understanding how we would show a health benefit when surrogate markers aren't available to measure such a benefit.

Perhaps we might consider something like changing or maintaining, or changing physiological function, because if we are talking about structure function claims, that is all you have to talk about.

I think if you get into health benefits, you get into incredible difficulty in trying to show that a health benefit has actually occurred. I mean all one has to do is read the health claims literature and the evidence that has been submitted there, and it's extraordinarily difficult.

I wasn't here yesterday, but after reading the literature, I found that there is not compelling evidence to show that there is a health benefit. There may be some evidence to show that there is some physiological changes perhaps or change in physiological function. We might

consider something like that.

DR. BENEDICT: Dr. Sigman-Grant.

DR. SIGMAN-GRANT: I think one of the things that I heard yesterday--and please correct me if I am wrong--was that there might be different benefits for different populations, the benefits maybe that have been shown with the preterm infants or some of the young children might be very different than you might see from an older population.

I seem to agree, why use these if these wasn't some sort of benefit to the user. How we define what that is may be reflective of what audience or what subpopulation they are being used for.

DR. BENEDICT: Dr. Hotchkiss.

DR. HOTCHKISS: At least as I interpreted what I learned before, and was reinforced yesterday, take diarrhea1 disease, it seems as though there is good evidence that certain organisms consumed have a positive health benefit on that particular symptom or disease, and how you would structure a claim or what claims you could make or what products you could introduce based on that, I am not sure, but it seems to me that the evidence is fairly strong in that particular case.

In other cases that we heard, most others, the evidence seemed to be much less compelling. So, it is a case-by-case thing.

DR. BENEDICT: Dr. Russell.

DR. RUSSELL: Wouldn't that be treatment of a disease, though, and if we are not supposed to be considering that, I mean I suppose that you could take it a step back and say that that is due to immunostimulation or modulation, which would be a functional effect, improvement in a functional immune function.

I mean I am just trying to get your thought on that.

DR. HOTCHKISS: As it was presented, certainly it was treatment of the disease, but if you look, the difference seems to be in terms of what kind of claim you make on it. If you claim, if you want to say it treats a disease, something that is a disease state, then, it obviously falls in the drug, but if you look at most, either structure function claims or supplement kinds of claims, they do not directly mention disease, but underlying that is most always a disease, so it depends.

In my view, if you are going to say it, if you are going to say it helps diarrhea in some way, then, you have made a drug claim. On the other hand, if you said that it helps maintain normal bowel function or something like that, then, you are in a different ballgame, but the underlying assumptions seem to me to be quite similar.

DR. BENEDICT: Ms. Richardson.

MS. RICHARDSON: As one of the consumer representatives, my concern is that we are talking about a mutual understanding of these terms and these products, and we have got this group of experts around this table who can't seem to come to a consensus about it, that keeping in mind what Dr. Grant said and what Dr. Clydesdale said, that if you are going to define it, and we can't say that it treats a disease, and we can't say that there is a benefit, it raises the question about what are we doing here, but also could we then look at using some terms that would lessen what we are saying, and perhaps say that it assists with certain physiological functions because then it is not a guarantee the consumer is not hopefully going to think that if I ingest this, you know, I am not going to get diarrhea.

DR. BENEDICT: Dr. Fukagawa.

DR. FUKAGAWA: I am trying to synthesize all these thoughts, also looking at it from the consumer's point of view and from a physician's point of view, either a pediatrician or someone then focused on the older person, a lot of consumers will want to do what they believe is in the best interests of their child or themselves, who may be older.

I think it can be a bit misleading to claim that these products have a definite health benefit. In certain

situations, it does help the physiologic function, but if anyone has been a parent recently, one knows that your definition of loose stools or diarrhea in a child is really quite variable based on your cultural background, your home, whether or not you are willing to change 10 diapers versus 20, and I think in some situations, the physiologic response, namely, loose bowel movements in an infant, is a normal expected physiologic symptom in response to an illness that does not necessarily need enhanced therapeutics, I mean, you know, won't get hurt, but then, on the other hand, may not necessarily improve things, in which case then the claim would be more along the lines of treatment, which is not what we are addressing.

So, I think staying along the lines of having potential impact on physiologic function seems the most reasonable and honest rather than claim that it treats a symptom.

DR. BENEDICT: Dr. Buchanan.

DR. BUCHANAN: Just a little caution here and then to sort of restate what I stated earlier. There is a differentiation legally in the definition of a drug versus a dietary supplement, however, Dr. Hotchkiss is correct, this could be in the eyes of the beholder and the claim put forward.

So, I would not try to spend a lot of time here

working up the distinction between a therapeutic agent and a dietary supplement. You will spend the rest of this morning arguing that out and really coming to no resolution. Just assume that there is a health benefit if that is what you are leaning towards, and then let us sort out whether it's a drug or dietary supplement.

DR. BENEDICT: Excellent.

Dr. Gaskins.

DR. GASKINS: A therapeutic benefit in diarrhea1 disease is consistent with an improvement in barrier function. Barrier function is one of the major physiological functions of the intestine, so in that sense, you could claim that improved barrier function is the outcome without specifying treatment of the diarrhea1 disease. I think barrier function is much easier to measure than microbial balance, and so forth. I mean you can fairly well describe barrier function and measure the effect of specific organisms on barrier function.

DR. BENEDICT: Dr. Hotchkiss.

DR. HOTCHKISS: I think, to change a little bit, the definition of the organism is extremely important in this. I would like to hear from the molecular biologists, microbiologists if the state of the art is sufficient to define organism as something beyond genus and strain of the normal taxonomy, can you write a definition that would

include something specific enough that there would be no question if the taxonomy changed, that you still had the same organism.

DR. O'SULLIVAN: If I understand you correctly, you want to see is it possible to write a definition that you can ensure a strain doesn't change over time?

DR. HOTCHKISS: No. That is part of it, but that is not really what I am saying.

DR. O'SULLIVAN: Because that would be impossible unless you sequence the whole genome.

DR. HOTCHKISS: No, that is not what I am saying. The taxonomic name given to organisms is in a state of flux these days as I understand it, very much so.

DR. O'SULLIVAN: Yes.

DR. HOTCHKISS: So, any kind of regulatory definition of a specific organism is subject to change if that definition is only genus and species it seems to me these days.

DR. O'SULLIVAN: That is correct.

DR. HOTCHKISS: What I want to know is could FDA write into their definition for a specific organism something that would not change if the taxonomy did change.

DR. O'SULLIVAN: That is a very good point, okay, because that is correct. When you talk about molecular speciation, it comes to a point how much different must the

equence be before you cross the barrier between species or ubspecies, et cetera, and that changes, and there is no umerical value that is across the board.

In some cases, people say 95 percent, in other ases it is over 99 percent, because it all depends on the ctual, how related this particular phylogenetic molecule s.

So, it all comes down to classifying, calling a pecies or subspecies as it is characterized on certain days containing these particular phenotypic characteristics which are important. If relying totally just on molecular axonomy is probably very naive because what is really important is the phenotypic characteristics, so a definition would have to include not just genus and species, but it would have to include an organism with this particular biography essentially. You will have to define a proper biography for a particular organism because the actual, even the genus names can actually change.

DR. BENEDICT: So, if I understand what you are saying, the answer is probably not.

DR. O'SULLIVAN: If you just say a genus and a species, that could be totally different in five years' time.

DR. BENEDICT: Absolutely.

We have other people on the list, but do you have,

Dr. Gaskins, a comment on this topic?

DR. GASKINS: However, there is an international set of guidelines. There is an international committee to name strains and species. Those guidelines are used by the International Journal of Systematic Microbiology was the former name, it now has a new name that incorporates evolution in the title, and I can't come up with the name, but there is a very specific set of guidelines that they follow, that is internationally accepted guidelines, and I think that would be a good place to start. It is not an ASM journal, it used to be.

DR. BENEDICT: Thank you. So, we are going to move to the people who are on the list. We have discussed viability, we have discussed ingestion. We have spent a lot of time on benefit, and I suspect we have gleaned about everything we can on the topic of benefit or not, and I think we have pretty well dealt with known or not known.

So, let's move down the list. Dr. Clydesdale.

DR. CLYDESDALE: I just wanted to go back to the comment that Dr. Buchanan made benefit. I just would like to reiterate that whether we talk about health or whether we talk about physiological function will not depend on the law in my mind, but will depend on what data is available and what we are comfortable saying based on the data.

DR. BENEDICT: Dr. Montville.

DR. MONTVILLE: I had more of a question in terms of the use of the definition, whether it is going to be for regulatory and technical purposes, in which case physiological function and barrier properties, and things would be very appropriate, or if it is supposed to be useful to the consumer, in which case physiological properties and barrier functions has no meaning, and intestinal well-being, although we kind of laugh at that, they think they know what it means.

DR. BUCHANAN: But that was the question, Bob.

DR. BENEDICT: Interestingly enough, Dr. Buchanan is next on the list to speak.

DR. BUCHANAN: We are seeking your advice, and the advice you just gave us is something that we will be cognizant of. Communicating to different subpopulations within our range of stakeholders is always important, and that is why we are not asking you to write a definition. It does have to be able to communicate to all of our people that are interested.

That is responding to that question. I did want to go back to Dr. Hotchkiss' question or comment, and I guess I would turn it around and ask the committee, based on the conversation and discussions that you heard yesterday, is it important to us to be able to define a probiotic, not probiotics, but a probiotic in terms of something more

pecific than genus and species, do we need to be able to pecify a single strain and be able to follow the identity f that strain, is that an important issue.

DR. BENEDICT: Dr. Sanders.

DR. SANDERS: With regard to the issue of strain nd definition of strain for probiotics, I think although icrobiologists are constantly frustrated by changes in axonomy, and certainly they happen all the time and, you now, it is as difficult for us as it was for anybody, I hink that the important issue in my opinion is that in the aboratory, regardless of what genus and species you call an rganism, we have pure culture techniques that allow you to efine a strain, and a think a good lesson can be learned from Lactobacillus GG.

That organism was patented as Lactobacillus acidophilus. It was later defined as a Lactobacillus casei, and now it is known as a Lactobacillus rhamnosis, but you can track the history of published literature on that strain because it was constantly identified as Lactobacillus whatever GG.

So, even though we are in a position to have the species and even genus of organisms that are used as probiotics changed due to taxonomic developments, I think as long as reasonable pure culture microbiological techniques are used, it is very easy to define a strain, and that that

strain definition then can sort of supersede all the changes in whatever species we have.

DR. BENEDICT: Thank you.

Dr. Sigman-Grant.

DR. SIGMAN-GRANT: I just wanted to say something about the benefits. We seem to focus specifically on GI benefits, but would that be limiting potential future benefits that probiotics might have, which haven't suggested, maybe have as much definition, so when you say physiological function, one might want to be careful whether we label that as GI function specifically.

DR. BENEDICT: Dr. O'Sullivan.

DR. O'SULLIVAN: I am a total advocate of using a particular strain, because there is no justification in saying a whole species can do a specific thing. However, if you look at the peer-reviewed literature, there does seem to be general effects that is not strain-dependent, just like, for example, if a person's intestine is compromised meaning the flora has been significantly depreciated, the evidence. suggests that if you get essentially what looks like any nonpathogenic organism there in high numbers, it can somehow promote the normal flora coming back with a lower incidence of diarrhea.

Now, if that is the general effect, it either is classified a probiotic effect or it is not classified. So,

if you just limit it solely to it has to be one particular strain, you are eliminating that potential general effect.

DR. BENEDICT: Okay. Let's try to focus this down and end it sort of, and with respect to the strain itself, I am sensitive to the general effects and the specific affects, and I think we have heard about tracking historically, whatever you call it, it does certain things.

So, perhaps we could offer an opinion, first of all, on how--the word "specific" comes to mind, but is inappropriate--how defined the organism or organisms should be when we are defining the stuff, and I don't know exactly how to phrase a question.

Perhaps we could just have an opinion on how many of the committee think we need to go down to the strain level, and if I may interject editorially, if we have the strain level, then, the general effects might be taken care of. I don't know enough to know to interpret what you have said. It's my fault.

Dr. Cohen would like to say something.

DR. COHEN: I have been stuck for about the last 30 minutes. It is hard for me to separate this from application, I mean to know what strain you are having in yogurt is very different from what strain you are having for a specific claim,' that have a very physiological or functional or therapeutic depending on what area you are

talking about kind of effect.

So, it is hard for me to sort of look at this in a Lumped fashion.

DR. BENEDICT: Thank you.

Dr. Clemens.

DR. CLEMENS: Dr. Cohen, I appreciate that comment because if you look at a pediatric application, we know that infants cannot tolerate d-lactic acid, but they tolerate l-lactic acid. Again, we have to be very specific on some metabolites, as well, as we characterize the strains.

DR. BENEDICT: But the other thing is if people want to make health claims, specific disease health claims, and that is Column A, and if they want to say well-being, that's Column B, and in either case, perhaps we just need an opinion about what we need to know about the organism in there. I don't wish to be obtuse, but perhaps we could just do another show of hands about how many folks on the committee would like to see it to the strain level and how many folks are strained by that.

Dr. Montville, would you like to make a comment before we do this?

DR. MONTVILLE: Yes. Steve, that is still very difficult, and I would suggest we split it out into maybe for specific health claims do you need a strain.

DR. BENEDICT: Excellent.

DR. MONTVILLE: Versus for a general effect, would genus and species be enough.

DR. BENEDICT: Okay. Let's do that. So, let's do the specific health claim first. How many folks on the committee would like to raise their hands in favor of to the strain level for a specific health claim? Dr. Clydesdale, please help me out here. I am not getting anywhere.

DR. CLYDESDALE: I don't know whether I am or not, but until we understand the mechanism of the effect, it is very difficult to make such a vote, because maybe the effect, I mean if you say if it's a health claim, it may be due to a general effect, you know, to a wide variety of microorganisms that are in food, and the balance of these in a particular strain may not matter so much.

I mean so without understanding the mechanism, it's a little difficult to say whether we need it or not.

DR. BENEDICT: Dr. Montville would like to respond.

DR. MONTVILLE: I will just counter. We were saying we know that this one does it, it has been proven with this one. You know, whether others do it or not, we don't know, and how it does it, we don't know, but we can guarantee if you use this one, you get the effect we have looked at.

DR. CLYDESDALE: In individual cases I would

completely agree, but to generalize across the board, I can't. In individual cases, clearly, but it is sort of going around in a circular fashion. If a particular strain causes that effect, then, we should define that strain.

DR. BENEDICT: Dr. Hotchkiss.

DR. HOTCHKISS: It seems to me that if there is a general effect that is broader than specific strains, it is very simple then to say we have demonstrated this effect with Strains A, B, C, D, E, F, or generalized things, and those kinds of things.

So, if you ask for strains, you cover that base, but if you go in the opposite direction, you don't cover that base, because if the effect is very strain-specific and you are not asking for strains, then, you have lost some information. So, you can go one way, but not the other.

DR. BENEDICT: Okay. Why don't we just not vote.

[Laughter.]

DR. BENEDICT: Let's just summarize and say that some folks are very comfortable with the idea of specific strains for specific effects. Some folks would like to suggest that in the general sense, general physiological effects, global effects caused by a number of things. They are more comfortable with a less strain-specific term.

Just nod your head if you agree with that.

Okay. Most people nodded their head. If anyone

would like to object, do so quickly because we are moving forward.

All right. Next on our agenda is, under A), Safety Considerations, No. 2)--this should get easier as we go along, folks, the hard part is over, okay, the hard part is over, you can all wake up now--the question: What scientific elements would be common to all safety assessments? All safety assessment in probiotics. Let's try to think of this from the host's perspective, consider the huge number of unknowns both now and in the future, and think about how FDA might safeguard against unintended effects of what they are doing.

So, common to all safety assessments, and as usual, I have constructed a list for you. We have talked about things, and I don't mean to say they are obvious because they are not, but we were told about them yesterday, so we all still have them in short-term memory at least.

Purity, identity, what are the excipients, capacity for gene transfer and genetic changes, potential for deleterious side effects on the immune or the inflammatory systems, effects within particularly sensitive subpopulations of individuals. People have mentioned the immunosuppressed.

We have discussed a lack of apparent data dealing with people who have allergies, that there is data, but it

doesn't suggest anything, and the question of toxicity in the general sense.

So, we are talking about the science that the FDA needs to think about with respect to safety assessments. So, in addition to or the things that I mentioned, perhaps we could open the floor now and discuss safety assessments of probiotics.

Dr. Montville.

DR. MONTVILLE: I would just like to ask how the GRAS status of lactic acid bacteria impacts on this, because I think most of us and people in industry have been working on the assumption that if it is a lactic, it's a GRAS, the safety is established. From everything we heard yesterday, and all the studies and anecdotal evidence, there has never been any adverse effects reported.

Is it really necessary to consider the safety of the organism kind of per se without the little specialized things of gene transfer, and blah, blah, blah, blah, blah, blah? That was technical blah, blah, blah, blah, blah, blah.

DR. BENEDICT: And there were six of them. Dr. Yetley, please.

DR. YETLEY: I will try to clarify. GRAS status is always for an intended use, and historically, the intended use for these has been for a food effect and what

you are now seeing, of course, is that their intended use is for a physiological effect on consumer rather than food.

So, to the extent that that would change the parameters that were considered, the uses, the exposures, that type of thing, I think then you have to start bringing those into consideration.

The other issue is that dietary supplements, of course, are exempted from the food additive rules, which includes GRAS, and you also have, as you heard yesterday, increasing interest in using these in infant formulas, and so that is likely to be an intended use that had not been considered originally, so the answer is sort of yes and no.

DR. BENEDICT: In addition to that, let's also consider the 4- or 500 or so species we heard about that we don't know anything about yet, many of which are anaerobic, of course, and can't be cultured yet, and so we want to be inclusive, I think, to think of as many things for FDA as we possibly can.

Dr. Hotchkiss.

DR. HOTCHKISS: I just didn't hear you say infectivity on your list that ought to be a consideration.

DR. BENEDICT: Thank you. Infectivity. Crank it up. What safety considerations do you want to think about? What about excipients? We hear that there are organisms there for a purpose. We hear that there are organisms that

are just there. We heard yesterday that folks will load up on something to give you a high dose of viable organisms, and it may not be the functional organism that you are interested in, just to say you have a high dose.

We heard that there are excipients in terms of things to keep the pH in appropriate place, things to keep the organisms either dispersed or together. Do we want to know? I mean maybe it's obvious. How detailed do we want to know in terms of safety what these things are?

Dr. Hotchkiss, thank you so much.

DR. HOTCHKISS: I will break the ice. That is an issue because I heard yesterday in some cases the organisms either by filtration or centrifugation or other process are isolated as what I presume are relatively pure organisms. In other cases, the organism and the media in which it is produced are concentrated by freeze drying or whatever, so that the ingested material contains the organism, but also the medium in which it was grown.

So, those kinds of issues have to be considered in any safety assessment. Are we talking about organisms, organisms in food? Are we talking about the milieu that they are grown in, and the purity of that culture, and a lot of other issues?

DR. BENEDICT: Dr. Clydesdale.

DR. CLYDESDALE: I would just second that. There

aren't too many food grade media, so I think anything that was grown in a food, and was then dried or desiccated or freeze-dried would be fine, but if it is grown in microbial media--which I haven't eaten for some time--I think that we would have questions about that if that was part of the excipients.

DR. BENEDICT: Absolutely, and one of the things we heard yesterday was that sometimes things are grown in milk products, and certainly freeze drying milk products can cause difficulties down the line for those who have difficulties with milk products.

Well, that was quick. Safety issues that have to be considered by FDA.

Yes. Dr. Cohen.

DR. COHEN: Where would the issue of history of usefulness--is that a factor that is considered under safety, since some of these products obviously have very long histories of use?

DR. BENEDICT: A fine question. It will be in the transcript.

Dr. Fukagawa.

DR. FUKAGAWA: Would these products be required to present information with respect to dose-response effects in a group of healthy individuals?

DR. BENEDICT: Is this in the topic of safety?

DR. FUKAGAWA: In the topic of safety.

DR. BENEDICT: Or in the topic of efficacy?

DR. FUKAGAWA: I am sorry?

DR. BENEDICT: Is this efficacy or safety?

DR. FUKAGAWA: Safety also. For example, if you consume, you know, five instead of the recommended three.

DR. BENEDICT: So, that would be should they be required to look at potential--poorly chosen word--toxic effects of overdose.

DR. FUKAGAWA: Right. That was just a question.

DR. BENEDICT: No, it's a fine question, though. It is something FDA will deal with.

What about do you have comments on whether this kind of subset, toxicity, as extended to specific populations of folks, immunosuppressed, infants, allergic individuals, other hypersensitivities, do we think FDA needs to deal with this on this basis, if something is intended for the general populace, do they want to make recommendations about if you are immunosuppressed, don't do this? Dr. Clydesdale.

DR. CLYDESDALE: Well, I think allergenic reactions or lactose intolerance are the kind of thing that we would see on any food ingredient, I mean requires labeling as it does on any food. Other than that, I don't think we should require more than what a normal food

requires in terms of those kind of reactions.

If you have something that is much more serious than that, then, it has to be dealt with, shouldn't be eaten.

DR. BENEDICT: Dr. Sigman-Grant.

DR. SIGMAN-GRANT: Again, because one of the subpopulations that has been mentioned is infants, where infant formula for the first six months is the sole source of nutrition, and if it is intended for that use, that safety needs to be well established because this isn't a normal--even though it is in breast milk, et cetera, et cetera, it isn't normal for that product to have contained it.

DR. BENEDICT: So, let's try to elicit a few more creative thoughts about safety if we go to 2(a) and 2(b), so the question we are asked is: What approaches and methods are available to evaluate the various safety concerns that have been raised?

Some of the straightforward things are tox in animals. We heard that some organisms don't do the same thing in some animals as they do in humans, cell culture models or things like cell binding, cell culture models for cytotoxicity, directly induced cytotoxicity.

Then, we heard a lot of very nice discussion about the molecular approaches to make sure that the organism that

you are putting in is the organism you think you are putting in, and I will list them: RFLP with pulse field gels, PCR, the gradient gels with PCR products, FISH, and in situ PCR, although we didn't discuss it, I would assume is a reasonable approach to certain subsets of things.

So, those are the methods that we were given, and are there additional methods that we could use, or can you think of methods that we don't have that FDA might want to support the development of? So, let's try to think of everything we can think of to help with safety in terms of methodology.

Dr. Clydesdale.

DR. CLYDESDALE: I am not going to help with that question, but I did have another one. The comments you just raised and the list you just gave is not going to be applicable to common food substances.

DR. BENEDICT: In what context?

DR. CLYDESDALE: All the safety issues that you just raised would not be, for instance, needed to be done with yogurt.

DR. BENEDICT: Well, that is the question, isn't it? Not with yogurt because we have used yogurt for a long time.

DR. CLYDESDALE: Exactly.

DR. BENEDICT: But if someone changes the organism

in yogurt or makes a supplement of another organism in yogurt, would you have to do it then? Suppose you use yogurt as a vehicle to deliver an organism to help with something else.

DR. CLYDESDALE: But if you are using yogurt as yogurt has been made for thousands of years, then, I don't think we have to go through the list that you have just described.

DR. BENEDICT: I do concur.

DR. CLYDESDALE: So, any food product that has a long history of use and is being made in the same way it has always been made, we don't have to be concerned with safety. There is a presumption of safety with those products.

DR. BENEDICT: Yes.

DR. CLYDESDALE: So, we are talking now about kind of extracting and concentrating and changing strains, and all of that kind of stuff, more in the supplement arena than in the food arena unless you make changes within the food.

DR. BENEDICT: Yes.

DR. CLYDESDALE: Unless you make changes within the food.

DR. BENEDICT: As long as the historical product has been maintained, I think that it is not something we have to deal with, but as we all know from the way people approach things, stuff will happen.

DR. SIGMAN-GRANT: Well, coming back to the measurement issues, and I will keep hitting the infants and the children because that is the population I am most concerned about, I think if you are going to assure safety, you are going to have to either look at some things that have been done in other countries as far as growth and development of infants to which these probiotics have been added to traditional products.

I mean that is a different kind of measurement, but it certainly would be indicative of the safety of use.

DR. BENEDICT: This is the Center for Food Safety and Applied Nutrition, so we are supposed to think safety here. So, thank you for that.

Aren't you worried about anything? Do you want your grandchildren to ingest something, and you didn't think of a way to help them? Dr. Cohen.

DR. COHEN: Well, I think one of the areas is the issue of surveillance for adverse effects, and I think there exists and there is continuing efforts to improve the efforts to detect things that are unanticipated either because of changes in production, populations, a lot of these things that we can't predict.

So, I always like to perceive the concept of surveillance in a concept of safety, whether you are talking about something that is a formal postmarket surveillance

that a company conducts or general public health surveillance to detect an incidence of something that is greater than would be expected.

DR. BENEDICT: Thank you.

Dr. Clydesdale.

DR. CLYDESDALE: I would assume that when there were safety questions, that these would undergo, not only that long and very good list which really reassures me about my grandchildren, that you gave, but they would also undergo the typical test of safety with no effect levels that food additives go through, which we currently have.

So, they would go through that list, and then if there were specific concerns, such as Madeleine has raised, or that you have raised, and there are a bevy of other modern tools of biology that we can use to check those things out.

DR. BENEDICT: I agree and what I guess FDA is asking us is are there things that haven't been mentioned that we haven't thought about, that we could add to the list that FDA could consider or consider developing in the future. It is trying to encourage folks to think about maybe things that don't exist.

DR. CLYDESDALE: I think some of those things would only become apparent as we became aware of what organism or what strain was being added, and how strange it

was and how new it was and what kind of potential it had, and I think that some of the tests might become more apparent as we saw what was added, and a declaration should always be made prior to someone--I mean if they are adding it, they should let people know, and they should check it out if it's new.

DR. BENEDICT: Dr. Sanders.

DR. SANDERS: What I was going to say is that regarding safety, I think the current approach with companies that are producing defined strains of probiotics for applications in foods and supplements, as well as biotherapeutics, has been a focus on evaluation of the safety of the strain, and some of those toxicology tests, the presence of antibiotic resistance, and if antibiotic resistance is present, they evaluate whether or not there is transmissible or transferrable genes that are associated with those antibiotic resistances, and those types of tests are done on the strain, but they are not really done on the final product that those strains ultimately end up in, and, the idea being that if you can document the safety of the strain at very high levels in these sensitive models, then, if you use that strain at lower levels or at lower doses than was in the public, you have a reasonable margin of safety.

DR. BENEDICT: Thank you.

Dr. Montville.

DR. MONTVILLE: Essentially, we are supposed to be thinking out to the future. What about the safety of genetically modified organisms? If we get to know the mechanisms and we know that they are associated with a specific gene in some weird organism that is hard to grow in food, and it is on a plasmid, shoot it into Strep thermophilus. It's food grade, food grade ta-da-ta-da.

Do we have to worry about that?

DR. BENEDICT: A fine point.

The last thing that I didn't mention was a comment I guess that I made yesterday about expression of genes using the ray technology to determine that actually the organism does what you think it ought to do by finding out that it, in fact, expresses the relevant RNA. Just to have it on the list.

Dr. Buchanan.

DR. BUCHANAN: I would like to sort of backtrack a minute. Tom asked a series of questions, and I didn't hear an answer, and I am very much interested in hearing the answer or opinions or comments or further exploring where you were going with this, and what the commentary of the rest of the committee members are.

DR. BENEDICT: Thank you. I didn't see even raised eyebrows around the table.

Dr. O'Sullivan, did you have a response to Dr. Montville?

DR. O'SULLIVAN: Yes. I don't think that should be an issue because if you genetically modify something, you change it. It is now a new strain, it has got a new biography, and essentially, the approval of strains should be on a case-by-case basis.

I mean whatever you do to it, you change it, so if you put in a new characteristic to it, then, essentially, it's a new strain, so then that particular strain would have to be approved separately based on the new characteristics that is has got. So, you can't put it in a general blanket, I don't think.

DR. BENEDICT: Dr. Hotchkiss.

DR. HOTCHKISS: I probably won't be able to go out late at night after making this statement, but it seems to me if this scenario of Dr. Montville went through FDA's current procedures and assessment process for that organism, are adequate to ensure safety of that, at least as we know it right now, it would become a genetically modified thing. It seems to me it would fall under a rubric that FDA published several years ago, and it seems to be quite adequate to me.

DR. BENEDICT: I see nodding of heads.

Yes, Dr. Clemens.

DR. CLEMENS: Thanks very much for the comment, Dr. Montville. There was an action article in Science September 8th regarding GMO organism production of medicinals and vaccines, for example, and it seems to me that that really is a drug characteristic, and not purview to actually a charge of this particular committee, but certainly should be considered by the agency.

DR. BENEDICT: So, just to summarize, it would seem that people are nodding their heads to the thought that if it's genetically engineered, its species and perhaps its strain characteristics change, it has to be reevaluated, and that the mechanisms in place for evaluation of any strain might take care of the problem.

Please feel free to object to anything I say.

On your list, we are now at are there any additional scientific factors that are relevant for safety in: special populations--we have sort of talked about that a little bit; novel organisms, this, we have addressed somewhat; novel uses, and food matrices.

Why don't we discuss them just at random. I hope there will be discussion. Novel uses, we haven't really thought about yet much, and food matrices.

So, what are our comments here for helping FDA deal scientifically with these questions?

Dr. Clydesdale.

DR. CLYDESDALE: I think in the food matrices, there is going to have to be some care taken as to whether a food matrices is designed to be a carrier only of the microorganism or whether it is designed as yogurt is, for instance, or for another product to allow that product to grow in a specific manner, and if it simply just a matrix to hold the microorganism, I think then we will have to look at it a little differently than we do the others, and that can be decided at a later time, but certainly there should be a differentiation between those two.

DR. BENEDICT: Thank you.

Dr. Russell.

DR. RUSSELL: A question would be does the food matrix change the ability to get the viable organism to the site of interest, either to benefit or possibly harm it. I mean it seems to me that again if we are talking about viable organisms, to begin with, the idea is the viable organisms are going to get to the point of interest, and if that matrix can affect that either positively or negatively, that should be ascertained.

DR. BENEDICT: Dr. Sigman-Grant.

DR. SIGMAN-GRANT: Pass.

DR. BENEDICT: What about novel uses, is there anything with respect to safety other than the obvious if someone comes to you with a new use completely unforeseen?

I can't foresee them at the moment, but I am sure there will be some. Is there anything we haven't thought about? To me, it is fairly straightforward, but then I am the least knowledgeable about this kind of thing.

Dr. Fukagawa.

DR. FUKAGAWA: I would think a potential novel use would be that organisms could be selected that might enhance your ability to metabolize and utilize specific nutrients, which then have a whole body effect, such as in the elderly, one of the big things that they all look for are things to maintain lean body mass or to decrease fat mass, and whether or not that would be something that one might consider in the future in terms of altering MOU, such that you can selectively absorb specific nutrients, which may then enhance performance or growth or whatever.

DR. BENEDICT: So if I might just continue to interpret that, you would suggest that in doing so, you might then enhance uptake of things you don't want.

DR. FUKAGAWA: Perhaps, correct.

DR. BENEDICT: And cause a negative effect physiologically.

DR. FUKAGAWA: Right. You know, if you say you should enhance the absorption of a specific amino acid that may end up being a precursor for a neurotransmitter that might have an interaction with the drugs that you are on for

your hypertension or something, you know, along those lines, which gets very complicated and is probably beyond what I would anticipate.

DR. BENEDICT: I think that is going to be a very reasonable question.

Dr. Clydesdale.

DR. CLYDESDALE: Just continuing, I think in the future, you know, as we understand more about the genome of the bug, we will be able to sort of ask people how they want to feel and give them the microorganism, and I think that whatever is produced in the gut will have to be carefully looked at as to exactly what it does.

Almost any protein you want, you will be able to produce, so in the future, that is going to have to be looked at very, very carefully. Also, the mode of intake. I guess the ingestion is what we are sticking to, but there are some interesting people out there. I can remember people sniffing B-12 not too many years ago.

DR. BENEDICT: Oh, my.

Dr. Russell.

DR. RUSSELL: There are several links between bowel disease and arthritis, and I could possibly see, although I don't see it now if this turns out to be something for inflammatory bowel disease, it may also turn out to be beneficial in some indirect way to rheumatoid

iseases, a totally novel use possibly down the way.

DR. BENEDICT: Dr. O'Sullivan.

DR. O'SULLIVAN: Obviously, I think it is very ertinent to try and foresee new uses and potential problems hat can occur because I mean probiotics has a very positive onnotation to it, and if someone dies, well, then ssentially, the whole thing falls apart.

One thing that struck me was the use of probiotics for wound applications, and that probably needs to be more arefully defined because there is lots of different classes f wounds. I am not a medical doctor, but I do know there s lots of different classes of wounds, and there is a very igh chance of an organism getting into your bloodstream and ausing a serious infection via that particular application, o that really has to be much more carefully defined than imply ingesting, because you don't want people to die.

DR. BENEDICT: Dr. Clydesdale.

DR. CLYDESDALE: Rather than physiological new ıses, too, there may be new delivery uses, and that sort of interacts with the food matrices, and I think that we would nave to be a little careful on that if we started to use, for instance, candies to deliver viable microorganisms. There might be a chance for dosage levels that are very high in young children or, you know, there could be delivery mechanisms that we are not thinking of now, and that we will

have to think about if they occur, in terms of how much they are delivering and chance of abuse, and that sort of thing.

DR. BENEDICT: Dr. Hotchkiss.

DR. HOTCHKISS: It seems to me obvious this is an issue that FDA will have to consider on a case-by-case basis. So, the uses or application of any particular organism will have to be defined by anyone seeking FDA approval or bringing this to FDA, and FDA will have to take it on a case-by-case basis.

In some cases, new uses may prove to be beneficial, and therefore FDA will have to be prepared to expand its approval of uses. In some cases, some of the novel uses may be less desirable, and FDA will have to be in the position of denying those kinds of uses.

DR. BENEDICT: Dr. Fukagawa.

DR. FUKAGAWA: Just thinking about the distinction between its use for wound, sort of promoting wound healing, in some ways our consideration for a denuded gut or an inflamed gut is also a wound. So, in some ways perhaps the loss of barrier is a wound in and of itself, so the recommendation of the use of these probiotics is not really as far-fetched as an infected wound, because I had a surgical procedure.

DR. BENEDICT: I guess we could expand that comment to bowel resections and other things that would be

ounds. Is that true? I am asking.

DR. FUKAGAWA: Well, I suppose at the site of--

DR. BENEDICT: It is not a disease anymore.

DR. FUKAGAWA: It is not a disease.

DR. BENEDICT: It's just an injury. Is that true?

DR. RUSSELL: You mean for healing?

DR. BENEDICT: We have sort of excluded wound healing as--

DR. RUSSELL: I think they were talking about open rounds yesterday. I mean that is what the pictures were of, and burns, and denuded GI tract would be more -- I mean I suppose it could be looked at.

DR. FUKAGAWA: I was just thinking of a broad definition of wound in the sense of denuded GI tract, similar to burns.

DR. RUSSELL: Sure, weeping of protein and loss of wtrients.

DR. FUKAGAWA: Right, and loss of barrier.

DR. BENEDICT: Dr. Buchanan.

DR. BUCHANAN: Again, just to help focus the discussion, one of the things that we do is that we provide guidance to industry, who are developing these kinds of products, about the types of data that they should be collecting and the types of things that they should be considering in terms of safety assessments before the

product ever comes to us.

So, one of the areas that we are particularly looking for here is what kind of guidance should we be providing them in terms of areas that should be considered for new types of products.

So, for example, are there any potential or any concerns about probiotic drug interactions or probiotic nutrition interactions, is there any potential for the consumption of these products to lead to the masking of the diagnosis of a disease state, any of these types of things that we may want to, possibly on a case-by-case basis, possibly just as general guidance, say if you have the following potential, these are the kinds of data that you should be gathering before you come and put it out on the marketplace or request that it go out.

So, again, some of them are maybe potentially just far-fetched of the items that I just gave, but any kind of scientifically based opinions on what is important for us to be communicating to the people that are putting these products out would be very helpful.

DR. BENEDICT: And maybe we should just add to that list, Dr. Fukagawa's suggestion of effects on drugs that are already being taken already on board, if we change the physiology, how does that change drug metabolism and dosage and other interactions.

So, with that very effective spur to our intellect, what sorts of scientific things do we want the FDA to think about?

Dr. Sigman-Grant.

DR. SIGMAN-GRANT: I guess this is another place to put in if we are talking about infant and infant foods, there is obviously growth and development as an issue.

DR. BENEDICT: Are you comfortable that Dr. Buchanan has said FDA should look at influences ,of one probiotic on another? He didn't say that, he asked you your opinion. That seems like it is logical. I am trying to get somebody to say something here. Dr. Fukagawa will always say something.

DR. FUKAGAWA: Well, I think we can always ask individuals if it is known, what products, metabolic products or gene products might be released into the gut, and then absorbed, that would then have potential interactions and effects.

DR. BENEDICT: How would we measure physiological effects, sort of unforeseen physiological effects?

DR. FUKAGAWA: Well, .I would presume, for example, the tripeptides that were reported to have blood pressure lowering effect and antihypertensive effect. One could look at changes in blood pressure obviously or an interaction with their already prescribed medications and whether or not

there is synergism or antagonism under certain conditions.

DR. BENEDICT: Dr. Clydesdale.

DR. CLYDESDALE: However, I don't think we need warning labels that say people shouldn't eat yogurt cheese and other foods at the same time. So, I think some care must be taken that these recommendations pass the giggle factor. I don't think we need that, but certainly if specific strains are isolated and something new is introduced, then, clearly, we have to look at that. But again I think there is a separation, there are certainly different levels of what we are talking about.

DR. BENEDICT: Dr. Clemens.

DR. CLEMENS: Dr. Clydesdale, I appreciate your comment on the giggle factor because obviously those run in medications, we have immunoinhibitors, so we know there could be a hypertensive crisis, watch for tyramine production by some of these organisms is a possibility.

I would raise the question that Dr. Fukagawa raised, that it is possible that some of these organs could be used to develop hydrolysates for the future, and we are now talking about hydrolyzing into peptides of protein hydrolysates, for example, and are those peptides going to have some type of biological, physiological response, so it is more than just the organism. We look at actually the end product and delivery of that end product.

DR. BENEDICT: Dr. Sigman-Grant.

DR. SIGMAN-GRANT: I think in one of the papers there was some mention of production of short-chain fatty acids in the gut.

DR. BENEDICT: Yes.

DR. SIGMAN-GRANT: So; that might be something else, the effect that might have.

DR. BENEDICT: So, all of these are excellent questions. The actual measurement and the actual prediction of drug interactions and other things is something that happens I guess like everything else does. You unfortunately wait until there is an adverse effect, I guess, for drug interactions and for things that are unpredictable with subsets of the population unless somebody wants to correct that statement.

Dr. Sanders, do you have a comment?

DR. SANDERS: I was just going to ask a question about how--I guess I don't see these particular questions unique to the area of probiotics. It seems that any dietary supplement, we would have to ask the same questions on, and is there something to be learned in terms of the FDA approach to the other supplements that could answer these questions, as well, or is there the same--I mean is there an established guideline right now for how we could talk about how Echinacea might affect physiology for drug interactions

or any of the other types of herbal supplements?

DR. BENEDICT: Let me return that question to you. It is I would think an easier concept if you are putting a defined substance into an individual and if you are putting an organism into an individual, and the metabolism of that organism might change once it gets there, and prediction of what things that organism does once it is in the gut can or cannot be made based on how defined the organism is.

So what we are talking about, I think, might be unexpected metabolic products or unexpected growth characteristics or competitive characteristics that might have a deleterious effect that, in fact, we can't even see.

Does that kind of help modulate your thoughts?

DR. SANDERS: What you are saying is there might be something specific to a microorganism being able to grow in situ that would have a special effect, but I guess I don't see. The question is really exceptionally different, the mode of action might be different, but in terms of understanding physiological effects, I mean it's a double-edged sword in some respects because the people who are excited about the development of probiotics for their positive effect on physiology have to acknowledge that, in fact, the exciting part of that is that there is a physiological effect, and then the reverse side of that is, okay, what now, if there is a definite physiological effect,

is there a chance then that there could be these interactions or other types of implications based on the fact there is an effect.

That is a tough question. I think within the context of use of these organisms, though, I think we have to realize that, especially for the use of the lactics, for the most part, you know, there is just such a huge documented history of safe use that that has to carry quite a bit of weight, it would seem, in terms of our concern about some of these issues.

DR. BENEDICT: Oh, certainly.

DR. SANDERS: And that it is not until maybe something very specific, like the cloning of some gene from an exogenous source or something like that comes into play that maybe we really have to look very carefully at some of those issues.

DR. BENEDICT: But then FDA will have to deal with that, of course, which is sort of why we want to push this as far as we can. If this is our only meeting, but our only chance to give FDA guidance, I think we have to try to think of as many unpredictable things as we can.

We all accept Dr. Clydesdale's giggle factor and the fact that lactics in yogurt and all of the other substances have been around for several thousand years,' in fact.

Dr. Russell.

DR. RUSSELL: Just a comment. I think I would agree with you, Dr. Sanders, about the analogy between some of the concerns for supplements particularly the undefined supplements of botanicals and herbals that I think FDA is struggling with in a very big way, and perhaps some of the same issues that are unpredictable because the chemicals are very undefined, don't even know what the active substances are, let alone mechanisms.

So, I think some of the problems that we are talking about here or trying to predict are actually quite analogous to some of the supplement issues. Maybe we can learn something from each other.

DR. BENEDICT: Dr. Sigman-Grant.

DR. SIGMAN-GRANT: Just a clarification. This actually deals with a definition. When we said "viable," do we mean viable all the way down the GI tract? I thought there was something mentioned yesterday whether it was could pass the acid and then go through the bile.

Is that implied in the definition, and if it isn't, does that create another safety issue if it indeed doesn't get down to, say, the lower bowel of the gut where it is supposed to be effective, but in some way due to some injury or something gets into the systemic? I am not saying this very clearly, but is that an implied thing in the

definition or does this then become a safety issue or efficacy, I am not sure. I am asking for clarification.

DR. BENEDICT: And I am the least likely person to clarify it, but it would seem to me that if we have said that it has to go in as a viable organism, that is what we have suggested, then, what happens after that, as you have said, will either be a safety issue, an efficacy issue, a localization issue, but we have just suggested that it has to be living and breathing at the time it hits the buccal cavity.

Dr. Hotchkiss.

DR. HOTCHKISS: That is what I meant when I raised the issue of viability this morning.

DR. BENEDICT: Dr. Montville.

DR. MONTVILLE: I just question whether it has to be living and breathing because if you have a freeze-dried culture, it is certainly resuscitatable and could be viable once it hits the GI tract, but then again it could just be a loag of enzymes doing its stuff.

DR. BENEDICT: Dr. Hotchkiss.

DR. HOTCHKISS: The issue of resuscitation was mentioned this morning, and I would consider that viable.

DR. BENEDICT: And so it is possible the Chair misspoke with the phrase "living and breathing."

Dr. Buchanan.

DR. BUCHANAN: In the discussion of resuscitation this morning, there was no mention about resuscitation within the intestinal tract. It was only resuscitation. So, that point was not made clear, and resuscitation within a test tube can be substantially different than resuscitation in the small intestine.

DR. BENEDICT: Very fine point.

Dr. Hotchkiss.

DR. HOTCHKISS: I would consider that an issue of efficacy if it is resuscitated in the gut and then there is an issue of efficacy, and I think that is a key issue, but a little bit different.

DR. BENEDICT: Let me ask, if it's a non-resuscitatable organism in the gut, does that put in a different category, one of dietary supplement, food additive, and no longer a probiotic, do we need to distinguish probiotic from dietary supplement, is it something that I have forgotten which of our speakers used this term, a frug between food and drug? Does this cause us more trouble that it may even be worth?

That's not true, but if we are going to revisit this before the break, then, let's think about what it is going to be and where it could be resuscitated.

Dr. Clydesdale.

DR. CLYDESDALE: I think to call it a probiotic,

it would have to be resuscitatable in the gut. If it wasn't, it doesn't fall within a probiotic, I mean--

DR. BENEDICT: It's a plant then.

Dr. O'Sullivan.

DR. O'SULLIVAN: The word "viable" means more than just something living. It can be dormant. It means the potential to reproduce. If it has lost all potential to reproduce, well, then it's nonviable. That would be the microbial definition.

The classic example would be an endospore. For example, the bacillus spores that are used as commercial probiotic products in Europe and Asia. You ingest a spore, and that is completely dormant, but it has the potential. There is no guarantee that it is going to germinate. So, you cannot put that stipulation that it has to germinate, but it has to have the potential, and then it's viable.

DR. BENEDICT:, Dr. Sanders.

DR. SANDERS: I agree with Dr. O'Sullivan. I think that the important issue relative to the definition of probiotic is that you are consuming a live microorganism, and that is defined relative to laboratory techniques that can prove viability or the ability to reproduce.

Once it hits your mouth, goes into your stomach and then in through the intestine, a variety of things can happen depending on the microbe, and the yogurt culture is

arguably the oldest "probiotic" organisms. When they hit the stomach and the small intestine, for the most part die, and they are not viable there, but they still can deliver quite strong probiotic properties, the most documented of which is the delivery of lactase to the small intestine for people who can't digest lactose.

So, I would not want to see a definition include viability based on the documentation that these organisms aren't viable once they hit the intestine.

DR. BENEDICT: But the word "biotic"--

DR. SANDERS: Well, my opinion on that is that it needs to be viable going in.

DR. BENEDICT: But we are discussing resuscitatability.

DR. SANDERS: Again, my opinion is that that would resuscitatability in vitro in the laboratory, but you need to be able to document that the organism is viable as a part of a food or as a part of the dietary supplement, and not once it hits the gut. You would eliminate Lactobacillus bulgaricus and Streptococcus thermophilus from the definition if that is what you did.

DR. BENEDICT: Are they not viable when they hit the mouth?

DR. SANDERS: They are bile-sensitive organisms, and they did when they are exposed to bile. They don't have

the membrane structure to be resistant to that.

DR. BENEDICT: But when they hit the mouth?

DR. SANDERS: No, I am sorry, when they hit the small intestine. What we were talking about before was in resuscitatability in the intestine, and I am saying in my opinion there is a problem with that distinction.

DR. CLYDESDALE: It does set up a bit of a conundrum, though, depending on what the efficacy is based on. If the efficacy is based on growth within the gut, and you tell a consumer to take this and it is good for you if it grows, but it may not, I think that maybe that's a message that we don't want to deliver.

So, if the efficacy is due to something else besides growing in the gut, then, that's a different story, so the conundrum is whether it is viable or not and where it is viable depends upon the claim that is being made and whether it's efficacious. So, there may have to be more than one definition.

DR. BENEDICT: Dr. Cohen.

DR. COHEN: One of the impressions from some of the presentations was that antigenic stimulation may have an adjuvant effect, so it seems to me that it could be a quite reasonable claim that you would have some sort of immune stimulation by consuming something that was not viable.

Whether it is not viable at the time it enters

your mouth, past the tonsil or the small intestine may not be necessarily to what the particular claim is.

DR. BENEDICT: Dr. Hotchkiss.

DR. HOTCHKISS: It would seem to me that there are two issues that are related that can be separated. One is the issue of viability in terms of ability to be resuscitated before consumption in a laboratory setting versus efficacy. If you define efficacy, which we haven't really addressed, but if you come up with a definition of efficacy, then, that is going to take care of, in my view, whether it is viable in the gut or not viable in the gut, which is really kind of a side issue, does it do something positive, and it seems to be the issue.

The definition of probiotic is another issue of what can you say this is a probiotic, and as I said this morning, it seems to me to be viability or potential for viability is important.

DR. BENEDICT: Dr. Clydesdale.

DR. CLYDESDALE: I have no argument with Joe's comment, only then I would say if we are going to say it doesn't matter whether it grows or not in the gut, then, why does it have to be viable outside the body.'

DR. HOTCHKISS: Simply to separate it, to be honest with you, separate it from thousands of other things out there that are produced by fermentation, and so forth,

to give probiotic a definition that has some meaning. It seems to me if you don't give it that viability meaning, then, it's no different than thousands of other things that are made by fermentation that ends up really being defined compounds, and so forth.

DR. CLYDESDALE: But if you are talking about delivering a health benefit, if there is a health benefit, and you can put it in a shelf-stable product where the organism isn't viable, you may be able to reach more people than if you had it in simply a refrigerated product in order to keep it viable.

So, if the viability really doesn't matter inside the gut, then, I don't understand why it is necessary to be viable outside the gut. So, again, I am not sure that in my mind I can separate the definition from its mode of action.

DR. BENEDICT: Are you recanting your earlier statement that it should be resuscitatable?

DR. CLYDESDALE: Not at all. I am just saying I think it is tied to mode of action because if we don't tie it to mode of action, then, we can just say, you know, you feed the RIP bug to anyone and let it do its work, if it does that work.

DR. BENEDICT: Dr. Buchanan.

DR. BUCHANAN: I basically was going to ask the same question as Dr. Clydesdale. It did not follow on a

logical sequence that if viability within the gut was not important, why viability in the original product was important, and since we have already worked something through, I think we may have to go back and revisit the original statement about the requirement for viability.

I also have to say we get back to a communications issue here, like Dr. Montville talked about earlier. I think if you went out to focus groups, and when you said someone was feeding you a live culture, the expectation was that somewhere it was going to continue to be live once it had been ingested, but certainly anyone that could provide more insight on that, it would be very helpful.

DR. BENEDICT: Dr. Russell.

DR. RUSSELL: As I understand it, none of these organisms colonize and have prolonged viability in the GI tract, so we are talking about matters of degree of viability in the GI tract, and even yogurt organisms to some degree, to a small degree, some of them are going to survive for a short time.

So, I think we are talking about matters of degree here, and I don't thing we have to go back and re-form that definition. The assumption is that at least some of them are going to be viable in the GI tract. Maybe the yogurt organisms have less viability, but some of them do survive for a while.

They have a short residence time as compared to other organisms that will have a longer residence time, and that it is important, if you are talking about changing more bifidobacteria, and so forth, it is important that those bacteria do, in fact, survive.

So, I think it is just a matter of sticking with the definition, but realizing that none of these organisms are going to set up permanent residence.

DR. BENEDICT: Dr. Sanders.

DR. SANDERS: I would concur with that. I think that is an excellent point, Dr. Russell, and I think that even though with the example of the yogurt cultures they might die when they hit the small intestine and exposure to bile, and, of course, you are right, that is a matter of degree. We all know that bacteria die and, you know, logarithmic reductions, it is not all or nothing.

Again, I worry about the issue of trying to tie intestinal tract resuscitation to this definition because there seems to be some evidence, for example, that certain yogurt bacteria may have an effect on decreasing Helicobacter pylori in the stomach, and so viability may or may not be required for that, we don't know, but again, if they hit the stomach viable and they have an effect there, but they can't be resuscitated in the intestine, I think that that is their mode of action.

I think you run into difficulty with trying to require this intestinal tract resuscitation because then again you eliminate those types of effects, as well.

DR. BENEDICT: Dr. O'Sullivan.

DR. O'SULLIVAN: On the issue of it having to be viable in the intestine or not, the probiotic concept, to get away from rigid definitions, has evolved over the last 100 years, and it essentially has evolved to include more things.

The concept includes competitive exclusion. For competitive exclusion, you need viability. Just because the available commercial isolates, which we have to a large part, have lost that ability, does not mean that there is no such thing as a probiotic organism without that ability.

If you look at any microbial habitat, you will get good colonizers, and obviously colonizers which have lost, or ex-colonizers, as it were, to have lost that ability so, if essentially you tried to limit it saying viability is not important, well, you are excluding essentially what the original concept of probiotics is, and probably is one of the more relevant concepts of the actual definition.

In the case of the yogurt bacteria, the Strep thermophilus and the Lactobacillus bulgaricus, they essentially reach the small intestine and then essentially they either just release their enzymes because of the

permeability of the bile or else they maintain some viability for a period of time and produce more enzymes. That is not clarified.

So, you cannot say that if get a yogurt and heat treat it and kill it, you are going to have the exact same effect. In fact, there are studies to say that that is not the case. So, essentially, the issue of viability is an important part of probiotic organisms.

I agree there are some specific cases where basically just a dead cell acting as an antigen may not require viability, but they are specific cases, but the general concept of a probiotic I think has to include viability.

DR. BENEDICT: Dr. Clemens.

DR. CLEMENS: I would appreciate comments by Ms. Richardson and Dr. Buchanan relative to consumer expectations. There is some really fine work conducted by Dr. Chris Brun at UC Davis, indicated assessed expectation by the local consumers, and, number one, the consumers expected viability and expected that those organism would be alive as they hit the GI tract; and, two, in their expectations of potential benefits, there was some benefit of digestion, particularly lactose digestion, and they expected some benefit in terms of immune function, and they liked the issue in terms of colds, but did not go beyond

that, so that is the expectation in terms of in the Davis area of California.

DR. BENEDICT: What I would like to do is take 10 minutes, not the prescribed 15. We didn't resolve--we resolved sort of in some people's minds viability when it hits the mouth. We questioned resuscitatable when it hits the system, viability before it hits the mouth, but less important afterwards.

These are the questions that I don't really think we have reached a consensus on. I am not sure we can, but take the 10 minutes, if you don't mind, to think about that. When we come back, we will have maybe five minutes to deal with that, and then we will move on to the health benefits, and perhaps some of this will begin to resolve itself as we are discussing those things.

So, it is 10:31. At 10:41 we will start.

[Break.]

DR. BENEDICT: Dr. Yetley.

DR. YETLEY: Just to perhaps give some clarification to some of the confusion that you had earlier, I think particularly maybe in response to Mary Ellen asking the question, don't we need to look at safety and efficacy for all types of ingredients used in supplements or infant formulas or foods, and the answer is yes, but what is different about this is what we wanted to say, okay, given

the fact that FDA needs to assess safety and efficacy, what is there specific about probiotics that we should be looking at.

If somebody comes in to us and wants to add a probiotic to a supplement or an infant formula or conventional food, the one that has a long history of use or one that is really novel, what is that checklist relative to safety that we should use relative to a probiotic, does that checklist need to be modified if it's a different organism, if it's for a different population, if it has something else that is unique, but what are the factors that we should be asking questions about and what kinds of documentation or consideration would we like to see relative to those factors, and that is true for safety, that is true for health benefit issues.

So, given a probiotic, what is our checklist when someone comes in to us? It also has relevance not only to the organism, to the food that is being added to, to the use it is being put to, but also has relevance relative to manufacturing process and controls to ensure safety, as well as retention of any health effect.

So, I don't know whether that helps or not, but we are really sort of looking for these checklists that would be specific for probiotic use.

DR. BENEDICT: It does. It helps a great deal. I

am sort of processing whether we should spend three or four minutes on this viability question, and then in the next section, which is health effects, incorporate these checklists that Dr. Yetley is asking for into a discussion of health effects, and try to really do focus on the kinds of things that FDA would want to ask.

So, why don't we just do what I just said. Before we do that, let's just once more get a final set of opinions delivered succinctly and rapidly on the topic of viability, and let me just recap a couple of things.

We have talked about whether the organism should be viable the minute it crosses the threshold of the body, and viability is either the ability to grow, metabolize, and divide at the point that it hits the mouth, or is the ability to be resuscitatable somewhere in the gut, and we ask whether that is necessary.

This is tied, of course, into the definition of the word probiotic, and if we think FDA needs a category for probiotics that is different from dietary supplements, then, viability may be the thing that is important. I am sensitive to the fact that industry would probably prefer it go into the dietary supplement category. I am putting words in people's mouths, and I don't mean to. Regulations are different.

If a probiotic is the same thing as vitamin C, if

t is the same thing as a product of chemistry or iotechnology that is put into the body, then, viability may e totally nonrelevant. If, on the other hand, the robiotic requires growth, requires to be viable at a articular place in the gut, then, viability is important, ut it goes beyond what we think is crucial. It goes to the oint of where it ends up being regulated or how questions nd up being asked.

So, I will put one more thing to you. Suppose omeone engineers vaccinia virus, which is by most irologists' terms not a viable organism until it hits the ut and multiplies in an epithelial cell somewhere, is that probiotic because it is or isn't viable, but is esuscitatable, whatever the word is.

I think that if we could just focus on whether it s going to be in a category by itself, probiotic, or whether it is going to be just another piece of a leaf or a itamin, then, that is a different thing, and FDA will probably disagree with everything that I have said, but if you think it needs to be a different category, then, you almost have to say viability is an issue, and resuscitatability is an issue, and if you think it is going to be the standard dietary supplement, then, I don't think viability is a factor.

So, I don't know how you want to deal with those

tatements, just focus your thoughts, but if we could uickly just hear what people think from the committee, et's say, then, we can move on to the question of benefits nd health effects.

Dr. Hotchkiss.

DR. HOTCHKISS: I think two points. First, the omments of Dr. O'Sullivan and Dr. Clemens bear repeating. eople think they are viable. That is the world's lefinition out there, and that is the way the thing is oing, and I think that is important to keep in mind.

The second point is that if you don't have some easure of viability or resuscitation, then, you put almost verything in this category. For example, if I have a fermentation process that produces a vitamin, and I then till off the fermentation, that the fermentation products ave that vitamin, and I either isolate it or don't isolate it. If you don't have the viability issue in there, then, it seems to me that becomes a probiotic, and I don't think that is anything that we want under that definition.

So, in order to differentiate this category of potential health benefit from other things, viability is an important factor in ability or resuscitation or potential in that, but it seems to me a vitamin made by fermentation, without the viability characteristic, becomes probiotic.

DR. BENEDICT: As does bourbon.

Dr. Clydesdale.

DR. CLYDESDALE: Joe, did you want to then say that it has to be viable within the subject, within the human?

DR. HOTCHKISS: No, for me that is not an issue, because that issue falls under efficacy, and I think most, maybe even all, probiotics, or a significant portion will be viable within the target organism, the human, but that is covered under a broader domain of it must be effective.

Granted, we should know the mechanism, and so fiorth, but we have to have some effect. If that effect comes by viability within the organism, fine. If it doesn't, that's fine, too. In that case, in my view, it is the outcome, the positive demonstratable benefit that is important.

But in order to categorize these products as something, viability seems to me to be important.

DR. CLYDESDALE: But what if I fed the vitamin A and the dead organism, and a viable one ex vivo didn't come alive within the human, what is the difference?

DR. HOTCHKISS: Well, that's my point. I don't think we want to call a thing like that a probiotic.

DR. CLYDESDALE: No, but if it's ex vivo, it is viable in a test tube, but once you eat it, it isn't viable anymore, because it doesn't grow or duplicate. I don't

understand the difference between that and the vitamin A example you gave, because neither one are going to reproduce and grow--if, I am saying--if neither one reproduce and grow within the human, I guess I don't understand the difference.

DR. HOTCHKISS: But you saying that the one with vitamin A will grow outside of the human, but not in.

DR. CLYDESDALE: I don't understand the benefit of something growing outside the human if it is not able to grow inside the human.

DR. HOTCHKISS: I could conceive of examples where that would be a benefit. For example, production of lactase.

DR. CLYDESDALE: But don't consumers really believe that these things will have some effect on their intestinal flora or at least be alive for some period of time, and some of their effects are due to being alive for some period of time?

DR. HOTCHKISS: I assume they do, I don't really know. I think they expect a positive health benefit. I don't know if they expect them to grow inside them or not.

DR. BENEDICT: Dr. Cohen.

DR. COHEN: It sounds like we are talking about a subset where essentially we are restricting the mechanism or claim to an impact of a living organism. For example; the comments made about competitive exclusion, you are really

talking about the impact of a living organism. When you talk about a fermentation, you are talking about a dead.

So, it seems that in the definition of probiotic, it is not just that it is a living organism, but that the effect is mediated or the claim is mediated by the fact that it's an interaction with a living organism.

DR. BENEDICT: Dr. Montville.

DR. MONTVILLE: I have to disagree with you, Dr. Cohen, because in the case of lactose intolerance, it's the beta-galactosidase, and one could give the living organism in yogurt, and they die, and release the beta-galactosidase and has the biological effect.

You could have freeze-dried lactobacilli, they die and have the effect, or you could take a little capsule of beta-galactosidase and it gets down to the intestine and has the same effect, but at some point I think one has to draw a line, and to draw the line of viable, you know at the mouth, this is as reasonable a place as any.

DR. COHEN: But, see, then I guess I have the difficulty in then how do you separate the alcohol as a fermentation product in the other example before, so that you get back to lumpers and splitters in looking at things, and is the issue to try to focus what we really mean by probiotic very narrowly or more broadly.

DR. BENEDICT: Dr. Clemens.

DR. CLEMENS: I appreciate the questions on probiotics in terms of viability. If we look futuristically, and you had indicated that, Dr. Benedict, that there are several studies out there, both in in vivo and animal models and in human studies that are very suggestive, perhaps not convincing, but very suggestive that the viability is not necessarily required and that, in fact, as some of the studies have shown, that heat killed through traditional thermal processing, actually may well deactivate the organism, but does not deactivate the effect.

DR. BENEDICT: So, we arrive at the same place we started. So, here is what I think we should do. There is a lot of very viable opinion in the record now on this topic. I think since it has been suggested that the Food Advisory Committee will be asked to comment on these things again, perhaps we should leave it to the FDA to focus the question on the basis of viability to something, after having thought about everyone's suggestions and everyone's thoughts, focus the thinking in a direction that we can address perhaps a different perspective of viability in the definition of probiotics.

I am not escaping--1 am escaping--but I am not trying to escape on the basis of anything other than I think we have said everything that can be said. and I think that we are not achieving, what I don't see anyway is a

consensus, so perhaps if the Advisory Committee needs to consider it a little longer at leisure at home, and FDA can focus our thoughts at a later time, and this will enable us to move forward in the agenda unless someone would like, especially from the FAC, would like to raise an objection to that hypothesis, or from FDA, if you want us to keep going we will keep going.

Dr. Sanders, do you have one last--

DR. SANDERS: I am stuck with the occurrence, an hour ago, where you took a vote and it was a unanimous vote that viability was an appropriate component of the definition of probiotic, and even though I think the points being raised are very legitimate, and it is very clear that there are many physiologically active components out there in the food supply, we have to decide, when we talk about probiotics, what are we talking about.

If you want to administer fermentation end products, great, it is just not, in my opinion, not a probiotic, so maybe before you just shelve the issue, maybe you could just take the vote again and see whether or not there is, you know, even considering some of the very important points that have been brought up, has the opinion of the committee changed.

DR. BENEDICT: We can do that. The reason it was resuscitated was the question by Dr. Buchanan about is it a

resuscitatable organism.

DR. SANDERS: Well, my understanding is the point was is the resuscitation in the intestinal tract an important component of viability.

DR. BENEDICT: Well, is resuscitation anywhere inside the body an important component of using viability as a definition.

DR. SANDERS: I thought I heard that they were specifically commenting on the intestinal tract, but regardless, you could use that then, but maybe that doesn't need to be even part of the concept of viability. Maybe you don't have to define that. Maybe that is what can be left for later is maybe a better understanding, but I think it's an important point.

DR. BENEDICT: That was sort of my take, yes.

DR. SANDERS: Well, I think it is an important point that in terms of moving forward, if we know what we are talking about, are we talking about the delivery of viable organisms or not.

DR. BENEDICT: But I think that was the--Dr. Sigman-Grant?

DR. SIGMAN-GRANT: I think we were talking about the resuscitability of freeze-dried organisms, so I think, in essence, it was alive, like in yogurt, and/or freeze-dried or something that could be activated in some way or

its components activated in some way in the GI tract.

DR. BENEDICT: So, revisiting with another vote, if the committee would like to vote again, it's the committee's decision. I honestly don't know that we are achieving anything by continuing to machinate when what we need is maybe a little more guidance or what FDA needs, they have gotten, and it's their ultimate decision in the final analysis.

Dr. Yetley.

DR. YETLEY: It is your choice as to whether you leave it and want us to think about it, or you continue to discuss it. I think from our perspective, it's what is sort of the common core for considering safety and efficacy questions, is it that you have an organism alive or dead, you the DNA or the cell wall or whatever it is, or is it necessary that you start with a viable organism at least at the point of ingestion.

So, what is it that sort of drives a common core of safety-efficacy questions, what is that sort of minimum unit?

DR. BENEDICT: A fine question.

Dr. O'Sullivan.

DR. O'SULLIVAN: Just a consideration. If the word "nonviable" is included for specific purposes like, for example, delivering lactase or other enzymes or proteins, is

to consider what happens when a bacteria dies. What actually happens is, and you put it on the conditions under which enzymatic activities can occur, it breaks down, so the length of time it is nonviable becomes a real issue then.

So, like if you just heat-kill yogurt, and then ingest it, you are not giving time for degradation events to occur, like you will find the degradation enzymes are generally the more resilient enzymes within an organism, and they essentially chew up everything eventually.

So, that's a very important consideration. If you include the word "nonviable" or "dead," you are opening up a whole new issue, I think.

DR. BENEDICT: Thank you. I don't even have a summary to offer you, but I think everyone is grateful for all the comments. I don't want to put words in people's mouths. I still hear the word viability as being important.

Yes, Dr. Clydesdale.

DR. CLYDESDALE: I am sorry, I would like to ask a question of either Dr. O'Sullivan or Dr. Montville. If you take an organism that is freeze-dried viable outside the body, is that a better delivery vehicle from what you just said of the enzymes and metabolic endproducts than taking an enzyme that is not viable, that is dead, assuming neither one of them resuscitates within the body?

DR. MONTVILLE: Couldn't say.

DR. CLYDESDALE: You can't say.

DR. O'SULLIVAN: If you are using, if you are just using a specific example of a freeze-dried enzyme--

DR. CLYDESDALE: Versus a heat-killed, a freeze-dried microorganism versus a heat-killed microorganism.

DR. O'SULLIVAN: Well, then, it's not in a food.

DR. CLYDESDALE: No, that's right, not in a food.

DR. O'SULLIVAN: Well, then, it's a capsule.

DR. CLYDESDALE: Right.

DR. O'SULLIVAN: Well, I am talking about in a food, because in a food you have conditions in which enzymes can work.

DR. BENEDICT: But we still come back to if it's freeze-dried and viable or resuscitatable, that's one thing; if it's heat-killed, and it was alive, that's another thing. How is it heat-killed and not alive anymore any different from coleslaw? I don't mean that in the facetious sense. Are we going to define this as something different or are we going to include it in something that we already have a definition for?

Dr. Gaskins:

DR. GASKINS: I can just summarize what I have heard, and it seems that viability going in defines probiotic. Viability coming out would relate to claims made efficacy, and that can be easily measured.

DR. BENEDICT: Dr. Russell.

DR. RUSSELL: I was just going to say I think Joe mentioned that concept before, and I am coming around to that the more I think about this myself, that it is really an efficacy question.

DR. BENEDICT: On that note, the next thing on our list are potential health effects, and we are asked to consider, and I think viability will raise its attractive head again.

What scientific elements--this is important--what scientific elements would be common in considering potential health effects?

We want to propose or to suggest the scientific structure. We want to suggest almost a checklist, as Dr. Yetley has suggested. We want to suggest these things and put them into priorities. What are the questions FDA should ask about health effects? I probably have the inevitable list to help focus.

Some things I think are fairly obvious from the very nice presentations we heard - identify, the word "efficacy" is the point. We need to think about effective dose, the proposed dose, the delivered dose, the dwell time in the system of either living organisms that have become colonization competitors or the products that we are talking about that are giving us the benefit.

I think we asked questions about synergy among various strains, not only the ones that we put in, but the ones that are resident, the effects of culturing and scale-up on the later characteristics, the effects of the delivery vehicle and its excipients, do these enhance the health effect or not, and if they do, you have to consider that.

So, with respect to strains, that is a list of thoughts that I gleaned from the various speakers, and then there are several other categories. We must talk about colonization, localization, and some interesting points have come up.

Colonization of various areas in the intestine appears to be different. Colonization of various target sites other than the intestine we probably decided not to discuss, strength of competition, and an important one, the ability to penetrate the mucus layer that we heard about yesterday. I mean is it really colonization or are you just achieving something in the mucus.

Are there contact molecules' receptors? We know that some bacteria make their own receptors for going into certain cell types. That's in vitro studies. Are there molecules like carbohydrates, proteins? Do the organisms Inter M cells, do they enter epithelial cells?

These are things that are probably much more detailed than the FDA wants to hear, but I am trying to give

you a recount of some of the things that were discussed. Effects on the gut lumen, impact on the resident organisms, the 4- or 500 we know about, and the 4- or 500 we don't know about.

Changes in pH, nutrients, competition for nutrients, vitamins, iron, carbohydrates, bile salts, absorption of minerals. Effect on the various syndromes. This is the real health effect - diarrhea, hypertension, cholesterol, all of the things we heard, Helicobacter in the stomach, carcinogenesis, effect on food sensitivities which are not allergies, and then the last ones are general effects on the host response - does the organism have an effect on the inflammatory system, which is not the same as the immune system, do they increase the inflammatory response to promote disease resistance or do they decrease the inflammatory response to help you with something like inflammatory bowel disease, and these are not necessarily mutually exclusive or inclusive.

The immune response is different. Antibody production, we heard a lot about secreted IGA, and there are other antibodies reasonably to be talked about. T-cell function, there are two kinds of T-cells, alpha-beta T-cells and gamma-delta T-cells, and the gamma-deltas are vastly different from the alpha-betas. 'Does the FDA need to worry about the effects on these things?

Memory responses, of course, are important. T-helper 1, T-helper 2 cells, are they going to help with cytotoxicity, are they going to affect--this is really at the detailed level, but where do we want to draw the line about what is the call-down list.

In addition to the immune system, are there effects on the epithelial cells? We heard that epithelial cells, when contacted, will secrete cytokines and chemokines and growth factors. We know that that affects the appearance or disappearance of the M-cell.

We know that that affects other things, the appearance of inflammatory responses locally. And in the effects of the delivery vehicles here, and the excipients on all of the effects of the immune system.

That will do.

The questions that we have are, first of all, that is clearly not everything that you guys can think of or that you heard in the presentations. The question is what is important to the FDA.

The first thing. What is the highest priority and what are the auxiliary things FDA must do, what is their checklist, what is their call-down? Do you want to divide them up into subsets and talk about what is important about the strains first and then what is important about other things? Do you just want to free-associate?