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FOOD AND DRUG ADMINISTRATION

CENTER FOR FOOD SAFETY AND APPLIED NUTRITION

FOOD BIOTECHNOLOGY SUBCOMMITTEE (FBS)
OF THE
FOOD ADVISORY COMMITTEE

Wednesday, August 14, 2002

8:30 a.m.

Harvey W. Wiley Federal Building
5100 Paint Branch Parkway
College Park, Maryland 20740

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P R O C E E D I N G S

Call to Order

DR. BRANDT: Members of the Subcommittee, you have on your table copies of the slides from the presentations yesterday, as well as copies of slides from two of the presenters today.

I will remind the four public speakers that we are going to begin at 9:45 with Ms. Macintosh followed by Michael Hansen, followed by Gary Bannon, followed by Bill Freese. I would remind all of them they have 10 minutes, period, at which point I bang on the gavel and the trap door opens and you wind up in contaminated food.

DR. LEHRER: Is there any opportunity to ask questions or not?

DR. BRANDT: No. If you are going to ask questions, we have a break right afterwards. You can talk to them during the break.

Dr. Jones is apparently ill and isn't here, and so she is being more or less replaced by the inimitable Dr. Maryanski, whom I am told will be very brief.

FDA Food Biotechnology Update

Dr. James Maryanski

DR. MARYANSKI: Good morning, Mr.

Chairman.

Yes, Dr. Jones cannot be here today, so we are going to do a slight modification of her presentation, but I think we will still cover the issues for you and give you plenty of food for thought, so to speak.

I am going to do two things this morning in a briefer amount of time than was scheduled for this presentation. One, I am going to spend just a few minutes giving you a little background on some of the recent events and things that are happening now relative to biotechnology at FDA.

This is just part of our attempt to give you background information to help you understand who we are, what we are doing.

[Slide.]

There have been several activities recently, some of which are completed, one of which is completed, others are just beginning, so we thought that it would be useful to tell you about some of these very briefly, not going into any detail, but the idea is to let you know about these activities because it is quite likely that there will be aspects of some of these activities that we will want to discuss with the subcommittee at some

future time.

The General Accounting Office, GAO, did a study on FDA's procedures for evaluation of bioengineered foods over the past year and they have published the findings of their report May 23rd. That report is available on the GAO web site, and we can, of course, give that information to you.

The interesting thing about the report, they looked very carefully at our procedures. They actually went through a number of files word by word. They also talked to various individuals both inside and outside of FDA, and the object was to see if we were basically following the procedures that we have set out for these foods and if those things would be reasonable.

I think they found that overall, we actually were doing a good job. They did, of course, make some recommendations, and that is the part of the report that you will find most interesting.

They were basically a recommendation, one recommendation is that FDA, of course, does not receive all of the information about these products, and they thought that it might be a good

idea if at least on some basis, FDA would go out and actually visit a company or request all of the information from the company and actually check it to be sure that the information did support the conclusions that had been given in the consultation.

We agree with that recommendation. We actually had a similar thought in our proposed notification rule, so that is something that we feel would be useful.

Their second recommendation to FDA was that they felt that our memos that we place on the web now, that describe our evaluation of the products, could do a better job of explaining to the public what our decision is, and we also think that that is a reasonable recommendation and will be looking at that.

So, we have these two recommendations from the GAO that we will be looking at. I think that is something that you may find that report interesting.

Just on August 2nd, the Office signed some technology policy, announced new work basically. They announced that the federal agencies were initiating some actions to look at field testing

requirements and early food safety reviews for crops that are under development.

These are crops that are in the early stages of development, they are not through all of the regulatory steps, but because of pollen transfer or because of seed mixing, it is possible that these crops that have not been through the full regulatory process could become components of food at some point on an intermittent basis.

So, the agencies are proposing steps to deal with that issue, and FDA's piece of that is that we will be developing draft guidance for crops that are intended for food use for developers to come in for an early food safety assessment, and that assessment will focus on the proteins that are new in the foods particularly with respect to potential allergenicity because, as you heard yesterday, we can't set a threshold for a low level of a protein that would be safe, and so we want to make sure that even these intermittent low levels of proteins would be safe in food and there will be no disruption of the food supply because small amounts may be detected in some foods at some particular time.

So, that is something we will be doing

will be developing that guidance over the next several months.

Another study which is just underway is a study that is initiated by the National Academy of Sciences National Research Council, and the council has a Committee on Agriculture, Health, and Biotechnology, and that committee is initiating a study sponsored by FDA, EPA, and USDA on unintended effects that occur in plants and their possible implications for the food, so this is getting at this question of can something unexpected happen as a result of the genetic modification, what are the steps being taken to ensure that those do not result in public health problems in the food and are there ways that that process could be improved.

So, they will be looking at recombinant DNA-derived plants in comparison to conventionally derived plants to try to sort out this issue of unintended effects. So we think that is a very important study and that will be ongoing probably for the next year or so.

We have already discussed the other items on this slide, so I think my purpose here is just to kind of give you a heads-up of some other things that we are working on that you may be hearing

about, so you are not surprised about these things if they show up in the news or you hear about them.

DR. BRANDT: Do you want to go ahead and do your summary?

DR. MARYANSKI: You want me to do my summary? I have another slide, sir, that I need to do.

DR. BRANDT: Oh, before that?

DR. MARYANSKI: Yes.

DR. BRANDT: Okay, I am sorry.

DR. MARYANSKI: How about three slides, can I squeeze three slides in, Mr. Chairman?

DR. BRANDT: Yes, sure. I am just going by what you told me.

DR. MARYANSKI: I know, I have to be very careful here.

[Slide.]

The presentation that was scheduled for this morning by Dr. Kathleen Jones was one where we were going to talk to you in more detail about some of the issues that are being discussed in the scientific committee related to the assessment of allergenicity, and these are issues that we will have to be taking into account, as well.

These are issues that deal with how we

assess the sequence of the protein, the issues around serum testing, the use of animal models, the use of degradation of these parameters. I think you have heard a good deal about these already. They are also discussed in the background paper, which is in your packet. I believe it is No. 6.

This is the paper that FDA has prepared and Kathleen was the primary drafter with a lot of help from various scientists in the center, but the second half of this paper deals with issues that we will have to be thinking about as we develop our draft guidelines.

I thought that instead of going through her talk before you, because I am not an immunologist as she is, so I think that what I will do is go back to the decision tree that Dr. Mayers showed yesterday to give you a sense of our thinking about the decision tree, so that you have a little bit better understanding of how we have come to where we are in the Codex and what our current thinking is, so that it will help you in your discussions.

If you recall, this is the decision tree that was evolved by the task force in Codex based on the earlier information and other decision trees

that had gone before. I am sorry, I want to back up, that is not correct. This is the Expert Consultation decision tree, because we do not have a decision tree as part of the Codex guidelines.

But this is the decision three that was developed by the Expert Consultation that was used in developing the Codex guidelines.

The decision tree was first published by ILSI, as you may realize from the background papers, so decision trees have been part of this thought process for some time, and I think, as Paul alluded to yesterday, we do like to have a visual kind of representation as a key to help us in our work. So, there was a lot of interest in continuing the idea of the decision tree.

One of the things that we felt was that it is useful to have a decision tree, and we are certainly not opposed to it. What we found is that there are certain things that have not made us feel comfortable about any of the decision trees we have seen to date, and I will explain some of those to you.

When we decided to initiate the Codex work, we thought that the priority, the first work should be given to developing the text of a

guideline, put down on paper what we think is the best guidance based on the science as we understand it.

Then, if we can derive a decision tree from that, then, we would do that. Now, we did not have time in the Codex process to get to working out a decision tree based on the guidance, so the sense I am trying to convey to you is FDA is not opposed to a decision tree, nor do we think it is necessary to have one, but it could be useful if one could construct one that would work in a way that would satisfy the needs for providing guidance.

Let me be a little more specific then about some of the things that we observed in this particular decision tree. One of the things that it does is that this consultation resolves some of the problems that had been in earlier guidance documents and decision trees.

For example, it gets away from the idea of what is a common food allergen versus a less common food allergen. We don't have to address that issue anymore, and that is very helpful.

The other thing this decision tree does is it gets away from the idea of directly addressing

human challenge studies, and that is something that is very problematic in many circumstances. For the large part, people are really not inclined to want to use those studies on a routine basis, so it gets away from that.

So, there are a number of things that the expert consultation did that resolved issues that it was asked to look at. When we look at this, you can see there are a lot of yes or no's here in terms of what one would decide and even early in the process, leads you to conclusions about something being likely allergenic.

When we make evaluations, I think it is more like we don't have a litmus test. You know, it would be nice if we did, we could just put the piece of paper in, it would turn either pink if it's a no and blue if it's a yes. We would like that. We don't have that. We have to make judgments, and in something like that, digestibility, there is always a question of how digestible and what are the conditions, and so forth.

So, we find that that is the reason for wanting to take into account a number of different kinds of information and to have some flexibility,

and not to necessarily just stop at the point where something about the sequence seems to be similar to an allergen, and not ask any further questions, so we felt that that was too rigid in the sense of the decision tree.

The other thing that is in the decision tree are some new things. We have here targeted serum and the use of animal models as for example, and things that we know are under development and there is a lot of interest in that, and we are interested in those areas.

Our sense has been up until now, is that these have not been fully worked out in terms of development, in terms of research, to the point where we can use them for regulatory purposes.

We were a little uncomfortable with actually having a decision tree where things flow through these where there is an expectation that one would always do these for every protein. We have seen, of course, almost 20 proteins to date. We are confident about the evaluations that have been done by those, that have not gone through some of these steps.

It is not clear to us whether those would add, whether they would be necessary, and I am not

trying to make judgments. I don't want to make judgments here about this, I am just trying to convey to you what our discussion was in looking at these decision trees.

So, that was the reason that we thought, well, let's set the decision tree aside. We are not rejecting it, but let's set it aside, let's go back and look at all the information and experience that we have had and then work in the Codex process to develop the text, and then from that text, then, we can derive a decision tree, that would be even more helpful, but we only have so much time in the Codex, and so we didn't get as far as a decision tree.

But I hope that gives you at least a little sense of how we have looked at this.

I just want to say a little bit about the issue of weight of evidence, because we are aware that there are already beginning to evolve different interpretations of this and it's no wonder, when you think about the words one can see that there is a potential for that, and we would like to avoid confusion. We would like to have it be clear what we mean if we use that term.

We had confusion on a term we used in the

past, "substantial equivalence," that some of you may be familiar with, and there was a meaning that was associated with it, but, in fact, if things are not really clear, people will interpret them differently and understand them differently. So we would like to have whatever draft guidance we develop be as clear as possible.

Weight of evidence in our mind is something we do all the time in the food safety assessment arena. When we are asked to evaluate something, it kind of gets back to the litmus test, we don't have a litmus test for most things. We have to evaluate a number of different kinds of information.

That does not mean that if there is one test that suggests that something is an allergen, and there are three or four tests that suggest that it is not, that we say, well, the weight says that it is not. That is not the way we would make the judgment, we simply would not do that. One test could be the one that would sink the ship, so to speak.

What we do have to do is make a judgment about whether any data that suggests something could be an allergen, is strong enough and

meaningful enough, and we realize that that is not the sort of kind of digital answer that would make us feel most comfortable, but most of the things we do in food safety and biological science is we wind up having to make judgments.

So, that is really what we mean by "weight of evidence," it is more taking into account all the information, and that is why the Codex is structured in a way that there usually are certain numbers of tests that are done in the first evaluation. We don't just do the sequence and stop there.

So, the idea is that there will be several different pieces of information, and that one should look at all of that. Any one of those might be enough to say no, it's time to stop here, this is possibly an allergen, but it may be that that would not be the case.

In terms of developing our draft guidance, then, this is draft guidance and what we will be thinking about is developing a document that will put forward what we think are the practices based on current science, that will provide industry with the guidance to address this issue in a way that is scientifically adequate to assure the safety of

these products.

This is guidance, this is not a regulation. In regulations, we codify something, we put down the specifications for safe use. It is very rigid, it is very difficult to change.

Guidance is different. Guidance is non-binding on the agency, it is non-binding on industry, and it is written therefore in a way that does not say thou shalt do this particular test. So, we will use words in guidance that bother Dr. Metcalfe.

He has said quite clearly that the Codex, for example, bothers him because it says "may" in a number of places, but that's a guidance document, Codex is also guidance, it is not binding on countries.

So, what will happen is for each country, we will examine the Codex guidance and will develop its own use of that guidance or not use depending on the case, but the goal, of course, is to put out something in guidance that people do agree to, at least generally, so that there will be some uniformity in the approach and therefore an understanding among countries about how to approach a particular issue in this situation, the

assessment of potential allergenicity.

When we develop our guidance, it also will be a document that is not as rigid as a regulation. It is something that will go out for public comment, that is part of the process, and at some point we could make it final or it can just remain as draft guidance.

This is an area where we all know the science is evolving, that thinking is evolving. I will be very surprised if the issues that we are thinking about today are resolved before I retire from FDA. I don't think that is going to happen, but I think what we need to do is come to a point where we can at least say this is our current thinking, and that is what guidance is from FDA.

It is our current thinking at the time, and we issue guidance, so that industry has the benefit of our thinking and the public understands what our thinking is, and the guidance has the advantage that we can modify it fairly easily through the public comment process if we feel that we need to in the future.

So, that is the goal that we are here for and I think that is the comments that I would like to make this morning, Mr. Chairman, if you want to

entertain questions now or later, it is up to you.

DR. BRANDT: Any questions, anybody? Yes, sir.

Questions of Clarification

DR. GURIAN-SHERMAN: I guess that I want to start with the GAO report, which I think I would like to clarify something about it because I was one of the consultants on that report and I think it is frankly quite misleading in terms of the representation on that report.

Most of the people that were consulted are four companies. There were two consumer groups supposedly consulted. I know the other consumer group had very little input, and most of our input was ignored.

We have made that clear in other fora, but I think that anybody who reads that report should understand, at least from our perspective, as well as consultants on that report, that it did not adequately represent consumer opinion.

I am sure beyond the couple of consumer groups that were consulted to some extent, there is a lot of opinion from other consumer groups that is nowhere in that document. So, I think if you read that document, you should read it with that

perspective.

There are a couple other issues. One of the things that you mentioned in that report was that the GAO reviewed several of the submissions. I think they said they reviewed five of them. They, by their own, at least in discussions with me, admission are not experts on the process.

I am not sure exactly how they reviewed those, but I will say that we now are in the process of reviewing 14 of those reports, and frankly, come to a pretty different conclusion. Some of those reports are not several hundred pages, as you said. We have several that are 10 or 20 pages, are very cursory.

Right now there is no standards as far as I can see in terms of what is submitted to FDA. Some of them did no statistical analysis for many things. You mentioned stability yesterday. One typical way of looking at stability over several generations is to do chi-square analysis.

Many, most of them did no chi-square analysis, several did, by contrast. Some of the companies are doing a more thorough job than others, but there is really no standard, and I think we need to give FDA a lot of detail about how

they should do these tests.

I think from a scientific perspective, you know, we only have to look at Starlink. What happened with Starlink through the SATs is that the company that presented that data was criticized for the way they did a lot of the analysis, and I was personally involved in some of that analysis.

They used monoclonal antibodies instead of polyclonal, so you might not pick up fragments that are digested. They didn't look closely at glycosylation or some issues about whether the protein was glycosylated that were not resolved.

There are a number of things in the procedure. I think, as scientists, we all understand that those can make huge differences in your outcome. I think the process right now is so vague and so open-ended that you can't draw conclusions about a lot of the data that is submitted. It is actually most of the time not data, and I think you only have to look closely at those studies to see the tremendous amount of variation in the quality of the submissions.

For the most part, you know, we have also looked at FDA responses to those, and there is very little response from FDA to a lot of those issues,

and I can discuss a number of them.

So, I think that really has to be taken with a big grain of salt, and I think without an actual approval process, I am not sure how much can be done because the agency does not approve of the safety of these products, but I think as an interim step, the agency needs to have a tremendous amount of guidance wherever we can.

I mean there are some areas that are just not resolved in terms of protocols, but also in terms of decision tree, I can appreciate the desire to have flexibility, but again because there is uncertainty about what the results mean, I think there should be some clear stops here.

I appreciate what you said about digestibility, for instance, and there may be situations where you have an ambiguous result, but even from the studies that have been presented, Jim's work in '96 and subsequently, several of those that are considered stable under those tests were digested after two minutes or eight minutes.

I think those kind of things need to be built in as explicitly as possible into the guidance, and granted they are not written in stone, but without it, the companies are largely

determining the process of how this is done, and they may do a good job in many cases, they may make mistakes in others, and I just don't think it gives them enough detail, and I think we should be doing that or at some point in this process.

DR. BRANDT: Other questions?

DR. ARIAS: I have a question. The power of any good predictive model, such as I assume that this decision tree is, is reflected in the outcomes that have been tested in some type of real-world situation.

Now, it is clear that no one is going to test prospective allergens in a human population, but given the discussion that I have heard over the last day, there are at least some animal models for potential allergenicity.

So, I am wondering had this model actually been tested and validated for its predictive power using prospective candidates through an animal model system to see whether predicted outcomes actually correspond to what the model says they should.

DR. MARYANSKI: That's a good question. I am not aware that anyone has actually done that specifically. Certainly, this is very new as you

can see, 2001, so this process, I am not aware of a lot of things that have been run through this.

DR. BUCHANAN: Actually, with Syngenta, with one of their genetically modified products over a two-year period using our system, and with the dog, which as I mentioned yesterday, there is a hierarchy of response.

It was an interesting study, and the results turned out suggesting that it is not an allergen.

DR. LEHRER: I had a question. You talked about the decision tree versus the weight of evidence, and it seems to me that some aspects of the decision process lend themselves, our decision tree lends itself well to that, whereas other aspects may fit in better with the weight of evidence.

Do you think that some type of combination of these processes, of these approaches is reasonable?

DR. MARYANSKI: I would not want it to come down to a question of should we have a decision tree or not have a decision tree. I was one of the skeptics back in 1992 when Dr. Call from our center, when we were putting together the '92

policy, said hey, we can do some decision trees to explain this guidance we are developing.

Another colleague and I thought, oh, no, we will never be able to do that in a way that will not raise the kinds of issues that--but she managed, and obviously, by the time we all pitched in, we have decision trees in the '92 policy, I think that they have been useful, so I do think decision trees can be useful, and it could be that either aspects of this could be done as a decision tree or all of it depending when one has the opportunity to really sit down and think about it.

DR. LEHRER: Also, do you know why sequence homology was put first in this process as opposed to using specific serum testing?

DR. MARYANSKI: I was not involved. This is from the expert consultation, so Dr. Metcalfe would be a better person to answer that. I really can't answer that.

DR. LEHRER: One last point that Jonathan asked concerning animal models, I think you raised a good point. I think that the problem is that these models are currently being validated. You really need to validate them before you take it to that step, and I would imagine or I would hope soon

that some of them will have reasonable validation in terms of reflecting the human experience, so they could be used for that.

DR. ARIAS: May I make a comment? My understanding is that the cosmetic industry for many years has been validating animal models for allergenicity and for organic materials now. I don't know if that would be consistent with the proposed expression of transgenic proteins, but nonetheless, animals have been looked at.

In regards to my specific comment here, is that if we are considering adopting as part or at least recommending the adoption to FDA of part or all of this decision tree--

DR. BRANDT: We don't have to do that today.

DR. ARIAS: Yes, I realize that, but I mean if that is one of the issues on the agenda, then, clearly we need to know more about the issues, the power of this model and whether it is predictive. I think that is going to be a key. You can't adopt a model without knowing its potential predictive outlook.

DR. LEHRER: They may have been using animal models for many years. There is a lot of

question about the validation of those animal models frankly, and particularly for allergy and especially IgE antibody responses that we are looking at. I think they look at irritant type responses. They may call it validation for allergy, but I am not so sure it is.

DR. KAPUSCINSKI: I guess I would like to make three comments. Last night I sort of revisited all these documents again and one thing that really struck me when I read the entire FAO/WHO joint report is that we really can't look at this decision tree just alone, we really do need to read all the supporting documentation.

When you read that, you see that this is really meant to be a guide for sort of thinking through systematically and also in what order you consider doing these tests, but then the supporting documentation is really critical and I would argue that it is very similar to what I imagine you would be looking for in the guidance document.

It has all the caveats, all the suggestions about, you know, it lays out the pros and cons of the different methodologies, different in terms of the state of the art, suggestions about ways to address them.

I think that is that, I mean from my perspective and from my experience with risk assessment methodologies and a lot of other areas, not only in other aspects of biotechnology, but also other technology assessments, this is a pretty proven way of moving forward.

I don't actually think that there is this big a disjunct between this decision tree and starting off with writing a guidance document. It seems to me that expert consultation would probably use that integrated approach, and it really comes out clearly when you read the entire document rather than looking at the decision tree alone.

My second comment is that it struck me as I was looking at the righthand side of this decision tree last night and then again hearing you talk this morning, that what I am sort of hearing you say is that you would like to have the flexibility to, for example, not just stop if you get a positive response in the sequence homology, and I have to just stop there and go automatically to that decision of likely allergenic, but like to have the flexibility to do other testing.

That would be a very easy thing to do, a fairly simple modification of the decision tree,

but still be able to hold onto I think some of the elegance of what is in here right now, and would simply be to create another arrow and give the option that you can either, after doing the sequence homology, choose to reach the decision that it is like allergenic or proceed to the next test, which would be targeted serum screen, and you could also add another arrow between targeted serum screen and the last box, which combines pepsin resistance and animal models.

Again, if you look through the published literature on risk assessment methodologies, decision trees are often designed, so that there actually is an option in the sense that burden is placed on the user of the tree to decide how much more testing do they want to do, and if you gave that option, I think it would also fit with the notion that FDA may want to come out at the end, in the guidance document, saying if any one of these tests gives a very strong positive signal, that is enough to sink the ship, but give the users the flexibility of combining tests.

My final comment has to do with this concern that all these methodologies are still being developed, there is a need for improved

validation, et cetera. Again, that is not unusual to this particular area. We deal with this in risk assessment all the time.

I would argue that that is exactly the reason that we need, number one, a fairly systematic methodology that everyone can look at and say, oh, yes, this is the steps we should go through with all this documentation to kind of add the devil in the detail stuff.

Then, we do need some sort of surveillance and ongoing research after things get approved, so that we can learn and, over time, improve the methodology, but we obviously can't just stop in our tracks and not do anything until the methodologies get improved, but I think this actually gives you, using this tool combined with surveillance on any kinds of products that get approved where there may still be some questions and combined with research, is the way to move forward.

DR. ARIAS: Another question regarding the decision tree, analyzing some of the same documents that Anne mentioned in more detail last night, as well, I came across the issue that right now perplexes me, and that is, looking at the decision

tree, it is apparent that a prospective allergen that has not been previously characterized and has not been identified in a population, because apparently this hasn't been studied extensively for large numbers of allergens systematically throughout different geographical and ethnic populations, might very well slip right through the screen particularly one that didn't have the anticipated resistance to pepsin that not all allergens have.

So, since our knowledge, as I gathered from expert testimony and these documents, is less than perfect on what constitutes an allergen, and there is many exceptions to these rules, I think we might want to be careful that we don't place too much weight in this decision tree, and as Anne mentioned, make sure that there are other facets that go into the evaluation.

As I mentioned before, I think certainly we want to try to validate as many of the predictions of this model, but one just looking at it, which is obvious, is that type of allergen that goes right through your screen and never be detected, right through the decision tree.

So, just multilevels are very important

for enhancing confidence, but each one of these really intrinsically is flawed, and I think we all recognize there is no probability coefficients assigned to any of these, there is no quantitation. In fact, I am not even convinced, in talking about sequence homology the other day, a contentious issue, where the cutoff is.

It sort of reminds me of looking at microarray expression data, you know, what is a clear difference in gene expression. Some people say 2 standard deviations, some say 3. It is really flipping a coin in some regards. The same things holds true here.

The variety of epitopes that may be present, for instance, in a specific allergen, that are only recognized, say, by a subpopulation of reactive individuals, may not necessarily be predictive for the other allergen epitopes that are, for instance, present in a novel protein, perhaps a transgenic one, so we can't necessarily rely on that, and then we have to use ridiculously large numbers of sera in order to enhance our confidence.

I think these are excellent beginnings, but I think we have to recognize there are

limitations. There is no assignation of probability or quantitative outcomes in this decision tree. So, as long as we recognize that and proceed, I think it acts as a good nucleus, but clearly, lots more needs to be done.

DR. BUCHANAN: For the record, I want to mention a workshop that was held last year in North Carolina. I don't believe we have heard about that. That was dedicated to animal models. It was organized by Dr. Germolec at NIEHS, and I understand that that summary will soon be published, and I think all of the candidates were covered at that time.

DR. BRANDT: They must have pushed dogs.

DR. BUCHANAN: In this case, the rats were ahead.

DR. BRANDT: Do you want to do your summary now?

DR. MARYANSKI: I think I am done for now.

DR. BRANDT: You are done for now.

Folks, we are ready for a break. We will take a break and then we will start you all off in 15 minutes.

[Recess.]

DR. BRANDT: Sue MacIntosh from Bayer Crop Science.

DR. MacINTOSH: Thank you. I am Sue MacIntosh and I am from Bayer Crop Science, but today, I am actually representing ILSI. In particular, I am the chairman of the Protein Allergenicity Technical Committee. In the next 10 minutes, I would like to share with you a little bit about ILSI and about some of the work that we have been doing over the last couple of years since ILSI was formed.

I will start out by giving you just a little bit of background on ILSI, if you are not familiar with this organization, because I think it is a rather unique organization.

[Slide.]

ILSI is a nonprofit, worldwide foundation established in 1978 to advance the understanding of scientific issues relating to a wide range of different topics, nutrition, food safety, toxicology, risk assessment, and the environment.

Also unique to this group is that it brings together scientists from all realms, from industry, from government, from academia, and also from the public sector to solve problems with broad

implications for the well being of the general public. Thus, the funding also comes from those same groups, from industry, from government, and also from foundations.

[Slide.]

I am not going to go into this mission statement because I am short on time, but this just focuses on HESI, which is where the Protein Allergenicity Committee resides, is on the HESI side, which is focused more on the environmental aspects and health.

[Slide.]

Finally, the Protein Allergenicity Technical Committee, the goal there was to advance the scientific understanding of different relevant parameters for characterizing the allergenic potential of novel proteins and biotech products.

[Slide.]

On this slide, you know, we have a lot of decision trees and a lot of discussion about decision trees, but I only have it here to really point out that we wanted to look at each of these different boxes, evaluate the issues surrounding those, and see what we, as a group, could try to understand or maybe clarify using some various

scientific aspects.

In particular, we were interested in trying to validate various methods as the discussion earlier this morning. There are many methods out there, different companies are using different methods, and when we put our heads together, we realized this and wanted to try to develop some protocols that could be validated and could be uniformly useful, not only within the U.S., but globally.

[Slide.]

So, what we have done is we have convened several different expert panels with many different academics and government people and also public sector, and we have come up with this set of different issues that we identified that was the starting point of then narrowing down into specific projects.

[Slide.]

I will just run through these. The first was the need for standardization of the methods for amino acid sequence analysis, and I don't think any of these are going to be strange to you. These are all topics that have been brought up over the last day and a half.

Uncertainty regarding whether IgE epitopes are missed by the current sequence comparisons. The need for standardization of the in vitro pepsin digestion assay. The need for scientific consensus on additional information necessary for proteins that would be stable to digestion.

The need for scientific consensus regarding usefulness of using broad serum IgE screens to provide a more complete allergenicity assessment. Finally, the need for more research to evaluate and validate animal models currently available for human allergenicity assessment.

[Slide.]

Now, from that group, we came up with five different project areas. One was molecular characterization, which includes the digestibility stuff. The sequence homology and bioinformatics, another project. Animal models to predict human food allergy.

The last two, we haven't gotten very far in those, but I want to name them anyway, because they have been identified by our group. Effect of protein prevalence in food, and that is that threshold question, and finally, the development of sera bank, another topic that was also raised

yesterday. Again, we have focused on the top three so far in the last couple of years.

[Slide.]

Now, I will go through each one and kind of give you an update on where we are.

The first on the molecular characterization, we held an expert panel, and those experts recommended that we develop a standard digestibility protocol, and that we then take this protocol and conduct a ring test at multiple labs with multiple proteins, which is the typical way that we validate an assay, an analytical assay.

Of course, the second item, which you saw in the previous slide, was expand the abundance comparison and evaluation to really understand thresholds and if we can come up with a threshold.

[Slide.]

Now, the in vitro gastric stability, we actually have now carried out an international ring study at the labs listed on the righthand side. You will see that aside from the tech providers, which obviously would be very interested in this process, we also had a couple other labs, the National Center for Food Safety and Technology, and

actually a couple of the FDA people are here that conducted that study, and also the CLB Department of Allergy, which is in the Netherlands, and then the National Institute of Health Sciences in Japan.

So, it really was a very large study. This now has been completed, the ring study has been completed, the data is being collected at this point, and we are now working on a paper that would incorporate, of course, all the people who performed this study.

[Slide.]

Just a little bit looking on the results, in general, we saw very consistent results, in fact, we actually were pretty surprised because usually, a ring study like this is not an easy one to do if you have ever carried one out for an analytical study, but they were fairly consistent in the laboratories around the world.

We did digestions of a standard set of proteins at two different pH's, pH 2 and pH 1.2, and while we saw a bit slower rate of degradation at the pH 2 than at pH 1.2, it did not alter the overall apparent sensitivity of the protein to digestion.

One aspect was the gel fixing and staining

procedures may affect the visibility of certain fragments, but again the apparent sensitivity of the protein to digestion was similar.

We feel we have been successful establishing a general protocol, and like I said, we are writing up the paper and we will go to an external peer-reviewed journal to work that through.

[Slide.]

Now, in the sequence homology expert recommendations, we had several different recommendations focused on databases to encourage a clear set of criteria and definitions for allergens that would be placed in such a database, and convene an expert group to actually define what that criteria would be.

Identify all available databases with a view towards synthesizing all information including specialized databases, such as when we start to understand more about T cell epitopes, perhaps a database could be developed with those epitopes and we could screen against that, and not just whole protein or sequences of protein.

We also want to encourage the development of database or databases that have links and

annotations to support that data. Right now, most of the databases don't have links, so you are not really sure why that protein was put in the database, and we would like to see a link to the literature.

Finally, utilization of 3-D structural data could be informative, and the exploration of this aspect should be encouraged, and, of course, again, we have talked about the sequences, linear sequences versus 3-D structures, and as 3-D structures become more apparent and we get a wider range of them understood on different allergens, then, I think this would also have some value.

[Slide.]

Now, we have worked actually with ECVAM, which is European Commission for the Validation of Alternative Methods, and they convened a group last year to try to develop this ultimate allergen database.

They are at the point right now of trying to determine funding for that data base, which of course, as you can imagine, is not just the expense of setting up the database, but maintaining it and continuing to add allergens into that database in a very structured fashion is also a very expensive

proposition, but I think it is an important thing for all of us to have a publicly available database for allergens.

[Slide.]

The final aspect, which we have just started really in the last year, was the expert panel that recommended that we needed a comparative assessment of animal models with allergens and non-allergens, which is often the part that is usually left out. It is using a variety of exposure scenarios.

So, we initiated the evaluation of a rodent model for human allergenicity prediction with a standard set of proteins using different mouse strains, comparing IP to oral routes of sensitization, evaluating results with and without the use of adjuvants, and also comparing different sensitization and challenge protocols using bioactive IgE as the primary endpoint, which is another very important thing that we felt was very important in an animal model.

[Slide.]

Of course, in order to even start that work or think about the work, is proteins, and that is a very expensive and difficult aspect is to get

a good supply of pure proteins.

We have now hired a lab in Europe, and we are now having purified proteins made there. We have chosen actually two positive controls or what we would have as known allergens Ara h1, Ara h2, and also beta-lactoglobulin, and then we also have a couple known non-allergens RUBISCO and Soy lipoxygenase, and these are being purified as we speak, and we should have them available in the next six months to a year.

[Slide.]

Finally, in conclusion, allergenicity assessment for novel proteins and biotech projects should encompass a comprehensive evaluation--I think we all agree on that--that assesses a variety of parameters.

To date, no single factor has been recognized as the primary determinant for allergenicity. So, instead, our scientific guidance has been to utilize a holistic, weight-of-evidence whether you use a decision tree or not, it still has to be a weight-of-evidence of all the different pieces of data that you have, that accounts for a variety of factors and experimental approaches for an overall assessment of the

allergenic potential of the new protein.

Thank you for your attention and I really appreciate having the opportunity to share what ILSI has been doing, and if you have any other questions, don't hesitate to come to me and I can give you more information, and also Carlos Thomas, who is our scientific director at ILSI for this project, either one of us can certainly help and answer any questions.

Thank you very much.

DR. BRANDT: Thank you for being here.

Dr. Michael Hansen of Consumers Union. I think we have a handout from him.

DR. HANSEN: Unfortunately, I don't have any slides or anything. If I would have known I could use them, i would have.

Anyway, thank you very much for the chance to present the views of Consumers Union, which is a publisher of Consumer Reports, to this subcommittee. We feel that the Food and Drug Administration is taking a very positive, important, and much needed step by undertaking an effort to develop a protocol for assessing the potential allergenicity of engineered foods.

We have already seen an example with the

Brazil nut allergen that was successfully identified and removed from and development stopped, so it never made it on the market. However, with that case and also with the subsequent case of Starlink corn, whose potential allergenicity was much more difficult to predict, these underline the need to have a sound, consistent, and comprehensive assessment protocol which, when scientific data is incomplete, errs on the side of protecting consumer health, to be used by all companies developing protocols and by all the agencies regulating them.

We feel that the guidance should be incorporated in the rule on Pre-Market Biotech Notification, which FDA has under development. Our comments are going to focus primarily on the specifics of what the assessment should contain and how it should be conducted.

As I note in my paper that I handed out, we think the FDA can profitably draw on several excellent bodies that have already given consideration and thought to the difficult question of allergenicity assessment.

I want to bring special attention to the global expert consultation that was a joint FAO/WHO

that was held in 2001 and chaired by Dr. Dean Metcalfe of the National Institute of Health, to the Annex on Allergenicity to the Guidelines for Assessment of the Safety of Recombinant DNA Plants, that Paul Mayers talked about yesterday, and to the work that the Environmental Protection Agency's FIFRA Scientific Advisory Panel. Their report on charging them with developing mammalian toxicity assessment guidelines for protein plant pesticides and with assessing the human safety of Starlink corn.

The key points that I would like to quickly go through is, first, we urge FDA, we think that the protocol should be a rule, and not a guidance. We feel that it needs to be mandatory and not voluntary.

Related to this, we also think that it is very important to have a decision tree because we think that in both of these cases, if you want the confidence of the public, they need to have some kind of sense that there is a clear-cut pathway that the companies have to follow.

A problem with having guidance, which is not binding on the companies or with having a general weight-of-the-evidence approach which says

you weigh these various things, that, to the public looks like that there isn't a clear pathway.

That is why we think it is important they actually have a decision tree, so it is very clear what data has to come in and what you will conclude based on those data. So, we do think it is important that you require the companies to actually do these tests, so that means rather than a guidance, it should be a proposed rule, so it is mandatory and that there is the use of decision trees.

We actually recommend that the decision tree to be used is the one from the Expert Consultation. We also view that all allergens, whether food, dermal, or inhalant allergens, should be used in the amino acid sequence homology searches. This is actually recommended in the Annex to the Safety Testing Guidelines that Codex put out.

We also think that all the assessment criteria that the Science Advisory Panel, that the Expert Consultation, and that EPA has suggested, that is, looking at amino acid sequence homology, digestive stability, heat stability, animal models and certain physical characteristics should all be

looked at, and as I said, these should be integrated into a decision tree.

We also feel that you should conduct tests on all, quote "all," quote "newly-expressed" proteins. That is language from Annex 1 of the draft safety assessment guidelines for rDNA plants that Codex has, and that means not just the intended transgene product, but also would include all unintended newly-expressed proteins, that is, the process of genetic engineering may turn on genes in a plant or animal that have been previously turned off, or the transgene protein could interact with the complex metabolic pathway to create new proteins, so all of them, whether intended or unintended, need to go through the same testing protocol.

We also believe that you should require that proteins be tested in both the purified form and as they exist in the food that will be sold, so also within the food matrix. We believe that the purified protein should be extracted from the plant from which the food will be derived.

We do not think the FDA should allow a company to test a protein as it is expressed in a bacterial or other microbial source because there

can be differences. For example, E. coli does not glycosylate whereas plants often do.

So, I quickly just want to make a few comments on the key assessment techniques for the amino acid sequence homology. I would just like to point out that the old decision tree that ILSI had, the Expert Consultation, they came up with a standardized methodology, and that is actually another important point is for all these assessment criteria, there need to be standardized methodologies and protocols.

For the sequence homology, what the Expert Consultation did is they started with the ILSI decision tree and then they updated it based on new scientific information. What they suggested is that rather than use the eight identical contiguous amino acids, and using a global alignment, the Expert Consultation recommended that you could use sequence identify of six rather than eight identical contiguous amino acids.

They also suggested using local alignments rather than global alignments when you are comparing unrelated proteins. They also suggested additional criteria, such as that 35 percent overall amino acid sequence homology is a cause for

further concern, and suggested development of databases and methods to test for discontinuous epitopes including those change by glycosylation patterns. They suggest that a very specific methodology, which I outlined.

I also would like to bring up the work, since they do refer to it, of Dr. Steven Gendel, who argued persuasively for the use of local algorithms rather that global algorithms when assessing allergenicity of novel proteins because those proteins are not evolutionary related.

DR. BRANDT: Three minutes.

DR. HANSEN: He goes on to develop what he calls a "biochemical similarity matrix," which divides amino acids into six classes based on biochemical characteristics, for example, hydrophilic acid, amino acids, hydrophilic basic amino acids, et cetera, and then the alignment of members of the same class is scored as a match.

The realignment was then confined to regions of 15 to 20 amino acids in each case to preserve the previously located identities. He actually found by doing this that there was significant sequence homology between beta-lactoglobulin and the Cry3A, which is found in Bt

potatoes, and between Cry1Ab and Cry1Ac and vitellogenin, and he concludes, "although it is clear that some amino acid residues are critical for specific binding, some conservative substitutions may not affect allergenicity.

Therefore, it may be prudent to treat sequence matches with a high degree of identity that occur within regions of similarity as significant even if the identity does not extend for eight or more amino acids. For example, the similarity between Cry1Ab and vitellogenin might be sufficient to warrant additional evaluation."

So, we think FDA should use the WHO protocol as modified by Dr. Gendel.

The only other comment I wanted to make, I will flip over to heat and digestibility because those are laid out, and I just want to, for animal models, bring people's attention to the meeting on Assessment of the Allergic Potential of Genetically Modified Foods, which was held in Chapel Hill last November.

I want to point out that one of the people that presented there was Dr. Katherine Sarlo, who is a scientist at Proctor & Gamble. It turns out

Proctor & Gamble, when they first started using enzymes in their detergents in the mid-1960s, they had huge problems with workers developing allergies, up to 50 percent of the workers in the plants were developing allergies.

So, what they did is they were able to use certain strains of guinea pigs and certain strains of mice, and the particular strains that they used were ones in which there was a direct correlation between the responses of the animals and the responses in the workers. Over the years, using those particular animal models, combined with medical surveillance of the workers and modification of the environment, they were able to drastically reduce this problem, so that the rate of sensitization dropped to less than 3 percent.

So, I think the experience of Proctor & Gamble shows that animal models can indeed work, and they can work with humans. We suggest that perhaps the exact strains of guinea pigs and mice that were successful surrogates for humans when predicting inhalant allergy of proteins, may be successfully used to predict food allergy.

We would suggest that if it hasn't been done, that FDA begin such research with known food

allergens with these particular strains of guinea pigs and mice.

DR. BRANDT: Your time is over.

DR. HANSEN: Thank you.

DR. BRANDT: Thank you, sir.

Dr. Bannon from Monsanto.

DR. BANNON: I certainly appreciate the opportunity to come and address the FDA on such an important topic and one that is near and dear to my heart, the protein allergenicity.

I come to you probably with somewhat of a unique perspective, and the unique perspective is due to the fact that I was an academic for 17 years working on food allergy, and now I am on the other side and working with industry, working on the same thing, allergenicity, and it gives you a fairly good perspective on what is going on and the science that is involved.

[Slide.]

To frame this for you, that you already are aware of, there are many issues that impinge on allergy research and allergy in general. As we have already heard, it is a fairly emotional topic. The numbers I have heard thrown around is in surveys, that 25 to 30 percent of people contacted

indicate that they or a family member think they have a good allergy.

Of course, the reality of that is quite different. We have heard that 1 to 2 percent of adults, approximately 4 to 6 percent of children actually have IgE-mediated food allergies.

Mixed into this, the fact that children do have allergies and can die from these allergic reactions, you have a very emotional topic that can sometimes overwhelm the science and cause bad science to be done.

Additionally, there are many stakeholders in this particular argument - industry obviously, allergists, scientists, regulators, food producers, and public, and they all have different perspectives and they all have something significant to contribute to the argument, but they come at it with viewpoints.

Also, we are in essentially a hazard ID mode at this point in terms of our decision tree and in terms of our determining whether a protein is an allergen or not, and we think that the hazard ID mode has worked very well, but we would like to see it move to more of a risk assessment mode, which I will talk to you about in just a minute.

Finally, and most importantly, the science of allergy is still evolving. Even though we have been doing immunotherapy for allergic disease for almost 100 years, there are still basic mechanisms that are lacking that we don't know, and it is still evolving, which is why we are here today.

[Slide.]

As most of you know, there is eight foods or food groups that account for greater than 90 percent of the allergies. They are listed on the slide. The biggest take-home message from this slide is that as you have already heard, the only way to treat this particular disease is by avoidance of the food, and therefore, that is paramount in our mind at Monsanto. We do not want to put allergens into food crops and put anyone at risk.

Of course, the U.S. policy designed to prevent that unwanted or unexpected exposures to offending allergens, and they do that by preventing transfer of existing allergens or likely allergens via biotechnology or other processes, and, of course, there are comprehensive labeling laws for all foods.

[Slide.]

Now, even though that is one big category, there are other categories. The first one obviously would be hidden allergens, as I have just described. The other category is alteration or quantitative increase of endogenous allergens, and finally, the big bugaboo, creation of food allergen de novo, new ones, and that is where the technology is lagging behind.

[Slide.]

We have many tools currently to detect known and potential allergens, and I have split them into two categories where we look at both known or cross-reactive allergens using bioinformatics, and you have heard a lot of discussion about sequence homology, six or eight amino acid window searches.

For potential allergens, we really have three tools - pepsin digestive fate, in vitro and in vivo IgE binding assays, and animal models, the last one of which is still under development.

[Slide.]

The tools to identify known allergens, bioinformatics, are really dependent upon the availability of high-quality clinical data describing the offending food and other allergens,

and that is absolutely paramount, and that information must be available to everyone, so that known allergens, proteins have been identified as allergens can be put into the appropriate databases.

Accessibility of that data, such as the gene or protein sequences, to assess allergenicity is also paramount, and I have given you an example of a web site, Allergenonline.com, which contains one of the more significant databases on allergens. It is curated on a yearly basis, and is housed out of the University of Nebraska at Lincoln.

Finally, there is another allergen database out of Europe, you have heard Dr. MacIntosh talk about that a little bit, that attempts to synthesize the clinical and structural biology data of what is a food allergen, and it is still under development.

[Slide.]

The bioinformatics, we have heard a lot of discussion about what that is and how to do it. The source of the gene is very important, very important to us, known allergen source, such as Brazil nut, we have heard an example of that versus a non-allergenic source will really determine, by

and large, what path you go down on the current decision tree, and will decide what tests are appropriate.

The appropriate search criteria. You hear Mr. Hansen talk about the global search, if you will, over the entire protein, and there are certain requirements that are already recommended, that is, greater than 35 percent identity over 80 amino acids.

The other is a small-scale search with defined amino acid window. We have heard a lot of argument about six versus eight amino acid sliding window. You should be aware that there are data out there, excuse me, that will be published this August in the International Archives of Allergen Immunology, that points to the eight amino acid window as being the preferred in the sense that six gives many false positives and the eight appears to include known allergens using the corn sequence database. That should be coming out, out of IAAI this month.

[Slide.]

Well, what do we need to do? We need to standardize our tools for predicting potential allergens, need to standardize the characteristics

of clinically relevant patient sera. It amazes me many times, looking at particular sera and how they are categorized as an individual being sensitive to a particular food.

There is not a common way of doing that at this point, although there is a best practice way, although it is not always utilized, and you see the problems with using a non-clinically relevant sera all the time.

We need to standardize our in vitro IgE binding assays. In the literature, you will find many different ways of doing our in vitro IgE binding assays and many ways in which it interpreted positive versus negative. That needs to be standardized.

Finally, we need to standardize our prospective standardization predictions. That means we need to look at the standardization of in vitro pepsin digestion assay and the animal models of oral sensitization.

[Slide.]

In terms of the pepsin digestive assay, you heard Dr. MacIntosh talk about the ILSI ring test. That addressed a couple of issues. One was some variables, such as the pH of the assay, and

the other was the reproducibility of the assay. Dr. MacIntosh did a great job of describing that, I won't go into that further.

The other question that has been brought up about the pepsin digestion assay is the biological relevance of that assay, and a recent publication out of my laboratory before I joined Monsanto indicates that stable fragments of food allergens contain some of the immunodominant IgE binding epitopes lending some biological relevance to the fact that the pepsin digestion assay appears to be able to identify fragments that will cause etiology of this disease.

[Slide.]

Validation of the oral sensitization models. I have been involved prior to joining Monsanto with the development of two animal models, a mouse model and a swine model. They used an intragastric sensitization protocol or an IP, intraperitoneal protocol.

What we need to do are listed on this slide. We need to have a high positive and negative predicted value, i.e., clinical accuracy. We need high correlation to clinical manifestations of food allergy.

We need relevance to the oral route of sensitization. That doesn't mean that it has to be an oral route, but has to have relevance to the human condition.

We need to be able to distinguish between complete and incomplete allergens. What that means is an incomplete allergen being one that can only elicit whereas, a complete allergen is one that can sensitize and elicit, and we need to be able to validate and have available test materials to validate those animal models.

My experience in the academic world is most of these animal models were developed to look at the mechanism of food allergy, not for what we need in the industry in terms of predicting whether a protein is a potential allergen.

[Slide.]

We believe that there is an opportunity to improve the current allergy assessment. We can do that by applying a risk assessment mode, something that toxicologists have been doing for quite some time, to the decisionmaking process in terms of allergenicity.

To do that, we need more data. We are not up there yet. We have to have threshold levels in

terms of at least elicitation, how much exposure there is, and assign some type of hazard ID to particular outcomes of the assays that I have already described.

The exposure validations should provide, then, a context against which risk managers can make decisions benchmarking against known food allergens.

[Slide.]

Finally, I believe we have excellent methods for identifying known allergens and preventing those transfers to food crops. We can do that very well.

We are refining, if you will, the old methods for predictive like pepsin digestion, as you have heard, et cetera, and developing new ones, hopefully animal models, but that are not yet validated, to predict potential allergens, and we have the opportunity to improve allergy predictions by incorporating risk assessment strategies to already available hazard identification methods.

Thank you.

DR. BRANDT: Thank you, sir.

Now, Bill Freese from Friends of the Earth.

MR. FREESE: I am Bill Freese, policy analyst, Friends of the Earth. We appreciate the opportunity to present comments today.

It goes without saying that the FDA's assessment of the potential allergenicity of novel proteins is only as good as the data on which it is based. In order to be truly science-based, any given assessment procedure must rest on data that are both accurate and adequate to the assessment task. Without such a foundation, even the best approach isn't worth too much.

What I would like to do is, in contrast to the kind of broad-brush treatment we have had about FDA's regulatory approach, I would like to look in detail at two consultations. I have distributed both my comments plus the two consultations. You should have those.

The first has to do with Monsanto's Bt corn event, MON810. If you would turn to Appendix 2, what I have basically done there is compare the FDA's Note to the File that is the consultation document on MON810, and molecular characterization study that was submitted by Monsanto to the EPA. This is an unpublished study, which only the EPA has seen.

First of all, I recognize that the EPA has responsibility for the--I am looking at the allergenicity of Bt proteins, but as Dr. Maryanski mentioned yesterday, the FDA also has a role, and that is to look at other possible alterations, for instance, unintended effects or nutritional differences, and that is why Monsanto also conducted a consultation with the FDA on this crop even though it's a pesticidal protein.

Basically, you can see in Appendix 2, there are three basic errors in the FDA's Note to File on MON810. I will just go through this real briefly. The first one is that the FDA assumes there is a complete copy of the Cry1Ab gene in the corn, whereas, Monsanto's study shows clearly it is only a partial gene, and what apparently happens is there was the transformation vector ruptured during the transformation process and only a partial gene was incorporated.

Secondly, the FDA assumes that there is a NOS termination sequence in MON810, and, in fact, Monsanto's study shows pretty clearly that that determination sequence did not make it into the corn.

It is interesting here to note that this

NOS might have played a role, according to the FDA, in directing messenger RNA adenylation, so the absence of that NOS sequence might have some implications.

Third, the FDA assumed that the protein was nature identical, that is, identical to the native protein found in the Bt microbe, whereas, in fact, what we have is it looks like an odd-length protein about 92 kilodaltons, about 70 percent of the folic protoxin.

I think what this example shows is the need for the FDA to demand original studies, not summaries, and in every case, not just in random spotchecks, as was suggested earlier.

The second example has to do with Aventis' male-sterile corn. Basically, it produces barnase, and barnase is expressed in the pollen and causes the pollen to be sterile, but as we know, even with tissue-specific promoters, you often have weak expression. The barnase could possibly end up at low levels in other tissues of the corn. Apparently, Aventis looked at this.

Their method for looking at this was to say basically, was to assume that any level of binding expressed in tissues other than the anther

would result in "abnormal plant growth." So the test was basically to look at the corn and see if there were any abnormalities, and that was basically their test to see if barnase was expressed in other plant tissues.

It seems to me that the FDA should have clearly demanded at least an ELISA assay to test for barnase. That doesn't seem like it would be so difficult to do, and it would provide better information. By the way, barnase is a toxin. It's a ribonuclease which breaks down RNA.

That is a second example, in this case, where the FDA perhaps could have demanded better data.

A second point I would like to make, I think this has been brought up a little bit, Doug Gurian-Sherman mentioned it. The FDA does not reach any independent conclusions regarding the safety of a genetically engineered crop.

If you look at the two Notes to File that I have given you, if you look at the conclusions, basically, the FDA merely conveys the notifying company's conclusion that the crop is not materially different than their conventional counterparts, and then says basically that the

consultation is ended. There is no affirmation that this crop is safe, no affirmation by the FDA that this crop is not materially different, only conveying the company's conclusion that this is the case.

I think that is not at all what most laymen think when they think of the FDA and their evaluation of genetically-engineered foods, and I think we really expect more from the agency. They should take a close enough look at these crops to be able to say with confidence that they are safe or at least not materially different.

Perhaps one of the reasons the FDA has been willing to say that is because they do only collect summary information and perhaps don't feel confident in making the affirmation. Again, that gets to the need to demand original studies instead of the summary information.

The final point I would like to make is about the examples of lack of coordination under their coordinated framework. Basically, I will again use the example of MON810 since that is one I am quite familiar with.

Basically, we have lack of information flow in two directions. One, that FDA could have

avoided the errors in its Note to File if it had just consulted with the EPA, which, as I said, add this molecular characterization study, so it would have been very easy.

The FDA wouldn't even have had to go to Monsanto to request this study. It could have gotten it from EPA, but apparently didn't do that. The EPA, in turn, should have consulted with the FDA during its assessment of the Cry1Ab protein expressed in Monsanto's MON810 and also Syngenta's Bt11 corn events.

DR. BRANDT: Three minutes.

MR. FREESE: As Dr. Hansen mentioned, Steven Gendel, who is here, has studied Cry1Ab and found similarity, sequence similarity between Cry1Ab and the vitellogenin and egg yolk allergen, and he found the similarity. He thought it might be sufficient to warrant additional evaluation, and unfortunately, it doesn't appear as if the EPA has taken that under consideration.

So, it seems like there is a lack of information flow in both directions, at least in some cases, and that clearly needs to be worked on.

So, just to sum real briefly since I have about minute, I guess, I would say demand original

studies, not summaries. Errors can happen. Companies can either conceal information or perhaps just fail to report things. Adequate testing should be performed, and I don't think, well, again the barnase example I think shows that.

Then, we need coordination between the various agencies involved in looking at the safety of these crops and potential risks.

Thank you.

DR. BRANDT: Thank you very much, sir. Thank you for coming and for the material. All of you had all this material from all four speakers.

Summary

Dr. James Maryanski

DR. MARYANSKI: Thank you, Mr. Chairman.

I will be very brief. Again, we would like to thank the committee members for joining this committee. We think that we are going to have a lot of work and interesting topics to do over the next couple of years, and we welcome this as the beginning of that process.

I think you have gotten the sense, if nothing else, over the past day and a half, that there are quite a few issues here. We brought one to you actually in terms of what we are actually

asking you to took at.

We brought one issue to you, but I think you have got an inkling that there are probably some other issues that you may want to discuss among yourself and with us, and that we are likely to ask you about over the course of the next several months and years. I hope that has been instructive.

We have not asked you to look at our policy per se or our procedures, but it is likely that we will be asked for that, that we will be discussing as things go forward. We have a process that has been through much the same kind of process we are having here in terms of vetting it before an advisory committee before we take it forward, and there are things about that, that some people like and some people don't like.

It is an interesting process because we don't use a process for these products that is a full, comprehensive scientific review for every single product, and that was a decision that we made in 1994 based on the kinds of products and the characteristics of those products.

So, it is very different than a food additive approval and the process, and that is

something that you will have more opportunity to learn about.

So, it is something that I think you need to look carefully at down the road. We hope that today you can focus on the issue of our project, that we are really beginning in the sense of developing draft guidance now on allergenicity and give us your thoughts to help us get started based on what you have heard.

As we have told you, our intent is then to go back to work to develop a draft guidance document that we will bring back to you before it goes public.

We wish you well. We look forward to your input, and we certainly again thank you very much on behalf of all of us at FDA that you are willing to engage in this process.

Thank you, Mr. Chairman.

DR. BRANDT: Let me make a couple of announcements first. This is a process that is just starting and all of you, but not me, will be able to carry this forward. I am just here for this one meeting as far as I know. I go back to the bench now.

Second, taxicabs to all three airports

will be out in front at 3:15, those you that need transportation. I know there is at least one, to Reagan, one to Dulles, and one to BWI. The rest of you are on your own.

Questions and Discussion

DR. BRANDT: You have the three questions we have been asked to address, and then we begin with Question No. 1, which has to do with the priorities, emphases, et cetera, that you think the FDA should be taking into consideration in their material as it comes from the Codex material that you saw yesterday and that you have a copy of.

One other thing, all of you should have gotten the extent of reimbursement, a very valuable document, so if you don't fill it out and sign it, you can't get paid.

The floor is now open. Are there particular aspects of this international document that you think FDA should particularly emphasize? Go ahead.

DR. ARIAS: After reviewing the Codex document, it was clear that there is a substantial investment of attention to issues that have not been amply discussed at this particular meeting in regards to GM plants, and that is, the

transformation process itself and so for unintended consequences.

I would note that there were several sections in particular that amply described some of those potential unintended consequences we have heard through some of the talks today, some of the implications of that.

I would like in particular to address the questions of unexpected allergenicities as a consequence of gene insertion. It is, of course, in the hypothetical since there are no specific examples that can be brought to bear on this question.

Yet, I think in any assessment of the prospects of using GM foods, I believe that the issue of the insertion of the transgene, its unintended consequences on local expression of neighboring genes, as well as the potential for altering global expression patterns throughout the plant have to be at least addressed at some level, and the Codex document does stipulate the number of specific steps in this process that should be examined.

In particular, the concern here is that insertion of a gene can influence the effects of

neighboring genes and since the process of transgenic insertion is, by and large, a random event, although there is some bias towards insertion actually into transcriptionally active regions of the genome, and, of course, the attendant possibilities for how that might in a number of cases create problems. It is yet unclear to me what the actual examples are currently through industry for how those insertion events are monitored vis-a-vis the Codex guidelines.

For example, I would assume that all genes are mapped to a specific locus and site in a crop plant when they are put into commercial production, however, it is less clear to me, as a consequence of that, how thoroughly the expression pattern of neighboring genes that could be affected by the insertion of a strong promoter element, for instance, like the cauliflower mosaic virus 35S promoter, which is widely used in the genetic engineering plants, might affect neighboring genes.

One, for instance, could envision such an insertion as affecting a gene that is involved in transcriptional control and thus having very significant effects throughout the plant, that may not necessarily show up as an effect on phenotype

or on development or on fertility.

Moreover, it is also clear to me, having come recently from the meeting of the American Society for Plant Biologists that was held in Denver last week, that the state of the art of looking at metabolic profiles of plants is still in its infancy. Because of this, it would be unrealistic to expect at present that we could look at global patterns, for instance, of various metabolites that might conceivably be affected by insertion of the transgene or expression of that transgene and its effect on metabolism.

Yet, I would think that in crafting any guidelines for future, we should certainly consider the prospects that unintended consequences of genetic engineering should be examined and thoroughly characterized within the state of the art, clearly can't ask industry to be held to standards that technologically are not available, for instance, metabolonics, looking at metabolic profiles.

Yet, the Codex document certainly does put a rather strong emphasis on this issue, and I think it should be one that we should deliberate on further.

DR. ASTWOOD: I just wanted to pick up on Jonathan's suggestion. One of the things that was not clear to me in our charge from the FDA is whether the scope of the activities strictly focused on the protein or whether we should also consider recommending back to the FDA, the need to develop guidelines on how to do the exact kind of assessment focused on allergy that Jonathan really suggests.

There are suggestions in the literature about how to do that. There are examples in the literature of how to do that, but I am not aware of any specific guidance on how to evaluate whether there have been changes in endogenous allergens in the target crop, obviously, would be crop specific.

So, whether that is something that would fall within our charge or not may need clarification. I think it is certainly an important topic.

DR. BRANDT: As far as I am concerned, it is certainly mentioned in the Codex. I don't see why it is outside our charge by any means.

DR. GURIAN-SHERMAN: To pick up on that, I know of at least one case in the literature where the different levels of endogenous allergens have

been measured. There is case with pepper, where some varieties don't even have the assayed allergen and other levels, so there is some beginnings of that, and I think it is something that certainly should be considered especially in the context similar to what Dr. Metcalfe was discussing yesterday about although we can't determine clear levels of sensitization or response, there is some dose response issue.

So, in that context, I think that should definitely be considered as part of FDA's task.

DR. ARIAS: I would like to point out that it is not that genetic engineering per se has, as far as the scientific community knows, any special risk associated with it compared to other methods, for instance, traditional plant breeding, which as you mentioned, Dr. Brandt, yesterday, can bring together various combinations of genomes or genes that can sort themselves out in rather dramatic ways.

In fact, the evidence to date shows that the only known unintended deleterious effect of moving genomes has, in fact, been observed in classical breeding situations where, for instance, glycol alkaloids have been detected in potatoes

that were made by standard crop breeding strategies.

So, I want to point out that I don't think that genetic engineering per se has any higher degree of risk, however, since we are putting together a guidance document that should I think encompass both intentional protein expression and its allergenicity, as well as any unintended effects, I think this would certainly be reasonable in its scope.

DR. BUCHANAN: In the experiment I referred to earlier, that we did with St. James preparation, we asked three questions - is the protein of interest an allergen, has the protein of interest become an allergen, and has the transformation process somehow created an allergen in another way, and that is an unlikely event, we felt, but possible.

In this experiment, we were able to provide the no answer to each of those questions. So, I think with our protocol with the dog, we are able to address those areas, and I wonder if it may not be possible also with rodents, that just one has to plan the experiment properly, but we were certainly able to do that.

DR. BRANDT: Other comments about Question 1?

DR. GURIAN-SHERMAN: I just would make a general comment, reiterate a point, and it has been brought out by several speakers and others about how FDA should look at the guidance, and I think the FAO consultation has a lot of value. Some other points that have been brought out I think have a lot of value.

The FAO, for instance, cites the Dr. Gendel's work in its guidance as something that can be looked at further, but I guess I would just, in this context, want to reiterate that given the uncertainties of some of these tests, we should err on the side of caution in making our decisions, and I think that while I again understand FDA's desire for flexibility, until we have more certainty, when we get certain results from some of these tests, and I am think Maryanski indicated that that would be the case, that the product should not go forward even though there is some uncertainty.

If you get a result in the digestive assay that considers a protein to be stable, there is uncertainty about whether it is actually an allergen, but there is at least a reasonable chance

it could be, and unless there is something definitive that suggests that it is not an allergen, I think there should be some again clear stops in the process.

I think that needs to be spelled out for reasons that have been discussed already about the uncertainties of industry and the public about how to proceed.

DR. BRANDT: Other comments about Question 1 and the Codex?

DR. LEHRER: I agree that there probably should be some stops, but I would hope that we would be able to have several criteria rather than just one. I think that is the problem in the past, and I think the technology is moving along and our knowledge of allergens is moving along, so hopefully, we would have several criteria.

I think also that we need to have a balance in looking at these different documents in which some aspects are highly detailed and others are too vague, and I think that that is going to be an important challenge to us, that we need to have structure and some detail in terms of having similarity, but on the other hand, I think we have to have some flexibility.

DR. KAPUSCINSKI: I guess I would like to briefly reiterate the point I made earlier this morning, but this time in response specifically to Question 1 and our charge, and that is, that I support trying to develop a guidance document that would contain a decision tree and then would have a lot of guidance text that would lay out, at the very least, options for different methodologies that seem to stand up to the current state of the art of the science.

One way that flexibility can be built in is to also provide the option that if a company thinks it has come up with a better methodology, it can present results from that and make a scientific case for why that is a better methodology, and that is a way that we can kind of keep building as the science is progressing, but I want to stress really strongly that the power of having a decision tree approach has really been pretty well proven throughout the field of risk assessment in assessing many kinds of technologies, and I think we should take the wisdom from that and build on that.

It gives you a systematic way of thinking clearly about which test you should do first. It

makes it easier to explain the rationale to outsiders including consumers. It has the power that if different companies are using the same sort of systematic structure, it will be easier for us to be generating data that then will be easier to compare, which will again help us to improve the state of the art.

I mean I think we need to recognize that one way we are going to move the science forward on this, it is not only going to be through traditional kinds of research, but it is also through well documented gathering of the actual empirical data that you gather when you do risk assessment, and if you can both have that well documented and if you are using procedures that are relatively standard, as much as they can be across the board, then, you can compare the data from that.

So, the data that is actually being gathered in risk assessment itself can contribute to moving the science forward, and that will be one of the real powers of relying on some kind of decision tree methodology.

Finally, as I pointed out this morning, I think some thought could go into considering

whether it be worthwhile to add some additional arrows that would allow, if we look at the righthand side of that decision tree that was shown to us this morning, allow the developer or the company to do more than one of the tests if they want to.

I think that could be done and still have some clear endpoints. Finally, I would agree with Doug that given the uncertainty in some of the kind of information that gets generated right now, we do need to be careful and err on the side of caution.

DR. BRANDT: Go ahead, Dr. Astwood.

DR. ASTWOOD: Thank you. I had a question for Dr. Kapuscinski about I was very intrigued by your suggestion this morning again as you articulated it, and I was wondering if one thing for the drafters of the guidelines to consider would be a tiered approach, which is a common mechanism in risk assessment, where the methodologies, you basically have a decision process, but some studies are essentially triggered by data development in previous studies.

DR. KAPUSCINSKI: Yes, and that is very common.

DR. BRANDT: None of that is going to get

captured if you don't talk into the microphone.

DR. KAPUSCINSKI: That kind of tiered approach, as long as it is structured and you can again, if it is thought through clearly, you should be able to capture it in a visual decision tree, and that is the power of those, that they are a representation of really clear thinking and systematic thinking, and tiered approaches are very common in risk assessment.

Now, I think some thought has to go into the details of that. I am not blanketly saying any tiered approach would work. We would want to look at how that actually gets developed, but conceptually that is a very powerful way to go, and it has worked very well in other areas.

DR. BRANDT: Other comments about Question 1?

[No response.]

DR. BRANDT: We will move on to Question 2.

Are there areas that you believe would contribute, that is, areas of research to this whole process of allergenicity determinations? Now is your chance. Yes.

DR. GURIAN-SHERMAN: First, there is a

recent study that probably a lot of you are aware of, that I think bears examination, a Pugh forum on biotechnology, did an assessment of federal programs on research in allergenicity and found several significant problems, one, minimal funding, inadequate funding, lack of clear goals, lack of coordination between agencies, and I think, as we saw yesterday, some of the agencies have somewhat different goals.

NIH is looking more at basic research. That is where a lot of the research is going on. FDA and EPA have very small budgets and they need more targeted research to help them look at how they can implement their guidelines, how they can best do the tests, validations of tests, those kind of things, and there is very little funding in that areas.

So, I would first recommend that FDA look at that. There needs to be a coordinating body. I guess FDA and EPA's Office of Research and Development need more funds to apply to research, but there needs to be some mechanism to try to coordinate that research and to get more research addressing the specific applications. So, I think that would be a start.

DR. BRANDT: My observation about coordination among federal agencies, that that is an unnatural act.

[Laughter.]

DR. BRANDT: But there might be a mechanism for doing it, but certainly during my years up here, I have never figured it out at least how to do it. You know, it is kind of like getting two departments in a university to coordinate their activities. As long as you put one in charge, they are happy to coordinate, but you have got to have somebody in charge, that's the problem.

Yes, sir, go ahead.

DR. BUSTA: I am not sure if this is part of the last question or this one.

DR. BRANDT: It doesn't make any difference, you can go ahead. We will let them sort it out.

DR. BUSTA: I think that in needs of research and under other considerations in the Codex document, I think the effects of food processing, the processing treatments, and the whole sequence of how these products are going to be handled should be taken into consideration, because they either enhance or generate potential

problems, or they may, in fact reduce them or eliminating them.

I think that the ultimate use of these items as a food are essential considerations.

DR. BRANDT: Yes, sir.

DR. ARIAS: I think in thinking of the future, the FDA might consider linking efforts, pre-existing efforts, with other federal agencies, such as the National Science Foundation, U.S. Department of Agriculture, DOE, et cetera, who are already looking at functional genomics of crop plants in a very systematic way, in particular, the sequencing of plant genomes for a number of crops will be I think greatly useful in regards to some of the points that I raised earlier in regards to the transgenic process itself, as well as leading ultimately beyond functional genomics, the expression of various genes in plants and the influence perhaps of the transgenic process itself will lead to more systematic efforts in the field of metabolic profiling, which I think also is likely to be the future in regards to nutritional compositions and effects of transgenic expression of various substances in crop plants.

Since these efforts already are underway

by a number of federal agencies, it is seems to me integration of such approaches would be a very powerful tool to exploit that information in databases that are being created.

I feel also that it is unreasonable to expect industry to adopt the burden of having to pull a sequence and characterize crop genomes although certainly that has been done by Syngenta. I think the ultimate outputs of those data are much better served when they are in the public database and have broad utility for a large number of questions that address not only the scope of this meeting, but I am sure many other issues that will come onboard to FDA in the future.

DR. LEHRER: I just want to respond to point 2. Absolutely, yes, there are areas of allergy research I think that FDA can help further, and I would say yes to all of the issues that were raised. We know very little about the some of the basic mechanisms. Food allergy, we don't even know the nature of the components that are stimulating food sensitization or even in some cases eliciting a food allergic response.

Digestibility has been discussed. I would encourage looking at real life situations, that is,

old foods in terms of stability or lack of stability of proteins.

We want to make the assays to be as similar as possible to human exposure. Animal models are essential. I have been encouraged over the last couple of years in that there are several groups that are moving in this direction, and I think that we will see useful animal models in the not too distant future.

Although an animal model of complete food allergic response would be wonderful to have, I think that it probably would be somewhat of an impossible goal to have something without any type of experimental manipulations, as has been mentioned earlier, and I think that it is more important for our discussions to have a model of allergenicity at this point although it is difficult, it would have to be balanced somewhat with knowing the unique type of exposures that one has to food allergens.

Serum testing again I think is important. It has been talked about developing serum bank. I think that would be very useful in terms of standardizing and making available the right types of serum to be used in the assays, and then

certainly sequence homology I believe can be very useful.

I think it is very important how this is defined. I think there is emerging information about epitope sequences and substitutions of these sequences that you can have one amino acid that will actually enhance IgE binding to an epitope, and if one was using the strict rule of sequence evade amino acids, or so on, this would be rejected, whereas, it could be a very potent or potentially a potent reaction.

In terms of how FDA should implement all of this, it really is certainly a challenge I think to FDA and to all of us, because of the way monies are distributed by the government in terms of research, and unfortunately, you almost get a runaround in terms of that.

The agencies that are interested in this, such as the FDA and the EPA, don't have a whole lot of money to support research. USDA, I think has more funding, but I don't know that they have funding directly for allergenicity. There may be some available.

NIH certainly has the vast majority of funds available, yet, to my knowledge, they haven't

directed funds in this area, and I think that that would be the best source of funding if one can not only convince them to have directed funding for this area, but also have study sections of individuals that are knowledgeable about these problems.

You can have money directed to a certain area. I have seen this in AIDS, for example, where they have put millions and billions of dollars into funding, but then if you have study sections that are basic immunologists, composed of basic immunologists, you are going to see money going toward projects that may not necessarily the questions that we are interested in.

I think all of these issues certainly need to be addressed and would help further our knowledge and allow us to make better decisions concerning the allergenicity of these products.

DR. KAPUSCINSKI: Just to add a little bit to the end of what Dr. Lehrer was just saying, my thoughts when I looked at this question last night was recognizing the difficulty of agencies cooperating.

I do know of some recent cases where an agency with regulatory responsibility, in this

case, a subcomponent of Department of Commerce actually collaborated I believe with NSF to develop a very applied competitive research grant program, and so it seems like it might be possible for FDA to do something like that in concert with NIH.

It may be very helpful to generate some of this research through a competitive grants program, which is pretty well shown to help get results fast. It would be just simply because of the competition and the pressure on researchers to get stuff published.

It is also a good way of having a lot of transparency in the research results, so that may be able to piggyback on some of the comments that Dr. Lehrer just made at the end of his comments.

DR. BUCHANAN: Yes, I would certainly support the need for additional support, and I think that the dogs eat 12 months, you know, day-in and day-out whether they are busy making IgE or not. So, it has certainly been a major factor in our operation to keep that going for the last 22 years.

But I think that my impression is that one of the goals of that North Carolina conference was to at least support for animal models in

interesting other areas, and I think it is needed, not just for animal models where it is sorely needed, but also for proteomics. I think we need to look at the proteomics in addition to the things that Jon has been mentioning.

I am involved currently in various projects on proteomics of chloroplasts and of wheat, and I think if we can look in the future and apply that to allergens, allergenic foods, that the future will just be very, very great, I really believe that.

DR. BRANDT: Well, I heard the word challenges used twice, and it reminds me of a former Secretary of Health and Human Services, then called HEW, and after about a month on the job, at a press briefing, he was asked what do you think about your job, and he said, well, what I have been faced with are some unsolvable problems cleverly disguised as challenges, so there are some of those for sure.

I mean there are examples of NIH and FDA doing some things together in the past, and I would suspect that this is an area that certainly could be explored. The lack of a commissioner may hinder some of that at the moment, but some of it

certainly could be approached, and I think without doing that, it is going to be very difficult for some of this research to really get done frankly, because I think the odds of FDA getting big chunks of research money are pretty slim for a while at least.

Any other comments about Question 1 or 2? We are going to finish here by lunch at the rate we are going.

All right. Development of draft guidance that may aid in enhancing public understanding. Now, there is a real challenge to get across. So, there we go. Go ahead, sir.

DR. ARIAS: I think it is apparent from discussions in the documents that there is a lack of an absolute standard even in the best case for analysis and determination of allergens, and so I think clearly what the public will want to be apprised of is this lack of absolute standards despite the fact that the decision tree gives a yes or a no, of course, it doesn't integrate probabilistic issues, which I think are intrinsic to the risk analysis.

So, we really can't talk about a lot of risk or a little risk. We can only say there may

be or may not be. I think that has to be defined. Also, the concept of substantial equivalence, which I think is in some regards going to be a slippery one for the public. I know it has been in part for me to define what types of terms we can use to best describe the model systems and the outputs that we are comparing.

Third, I think the public, in general, has a great degree of confidence in U.S. regulatory agencies. I think they have, in the main, performed admirably, at least as a member of the public I am speaking, and the FDA in particular I think is obviously showing a high degree of sensitivity by this in other fora in trying to address those concerns and by the public comment, for example, and input.

I think what the public wants clearly are the facts and the truth. If we are ambiguous about our determinations, we should probably make it clear that those models and the improvement, the state of the art, this is the best we can say. I think if we go beyond that, we might very well wind up in the case of like the British public and their apparently lack of confidence in British health administrators vis-a-vis the bovine spongiform

encephalitis epidemics, the French Red Cross, and many others where public confidence has plummeted because people assured the public of risks that, in fact, did exist, but did not really communicate that effectively.

I think the public in the United States will tolerate some ambiguity as long as we are front and center on that.

DR. LEHRER: Also, I think it is very important that the public first understand what allergy is and the risk of allergy from their food supply, because I think that there is some confusion, as has been mentioned I think in the lectures yesterday, a much larger percentage of the population think they have allergies than really do.

Also, there are a variety of types of reactions or symptoms that are really not related to allergy, that they may attribute to that. So, I think that if in some way they can be better educated with regard to that.

Also, in dealing with allergists, I felt in some ways they might be one of the first lines of inquiry or individuals who may have reactions, and one of the things that we have tried to do at

the American Academy of Allergy is have sessions, so they better understand the process and also the assessment of them.

I would encourage that to go further because a lot of the folks that may be having reactions or think they have a reaction, if there is one, may go to their allergist and a lot of times they may not know how to deal with it or even how to discuss it with their patients.

DR. GURIAN-SHERMAN: I would like to reiterate and endorse a lot of what Dr. Arias said, and I think one of the ways to enhance consumer confidence is to lay out in as much detail as we feel is warranted by the science, what FDA is doing and how they are doing it, and what their criteria are.

I think a lot of the ambiguity and vagueness in the current process only lends itself to more consumer skepticism when it is examined closely. So, again, I would make a plea for as much detail as we can put in the process and to make it as mandatory as we can.

I know our charge here is to discuss it within the framework, but I that especially given the fact that there is not a natural pooling

process, makes it even more important to be as thorough and specific as possible in laying out the process.

DR. KAPUSCINSKI: I will just add that I think that if you actually intelligently present the decision tree picture, then considering the comments that others have made here, that is actually a really nice way to be able to explain to the public what FDA is doing.

People will be able to relate to that better, and I think it actually gives you an opening to communicate the message about ambiguity in a way that that will sort of make sense to people, because they will see that yes, there is these ambiguities, but instead of just being paralyzed by it, we are trying to move forward in a systematic way, and I think if it is articulated well, it will be easy to explain, to convince people that this is the best that we can do at this time, this is the state of the art.

I think again specificity can be in the more detailed text that maybe not every consumer will read, but it is there for the people that are more interested and want to read that. So, I think that the more you can show that the FDA is taking a

systematic, structured approach it is expecting across the board, the easier it will be to address Question 3 about enhancing public understanding. People are just going to be more comfortable with that.

DR. BRANDT: Other comments?

DR. BUCHANAN: I think it has been said before, but, but I will just say it another way. I think that certain of these technologies and protocols for testing really have to grow up as the field develops. That would include not only animal models, but the serum bank and perhaps other aspects of the decision tree.

I am optimistic if the work in the field or research in the field can parallel the development of regulatory policies, otherwise, this, as has been said before, it will just stop and anything would be terrible, that would be the stop.

DR. ARIAS: I think also it does the FDA no good to bury its recommendations in obscure text like the Federal Register and such, which the majority of people don't read every day. I think there are a number of venues for the FDA to more amplify their message to the general public in

particular, for instance, societies that deal with plants and plant biology, such as the American Society for Plant Biologists.

There are a web sites, of course, that deal specifically with information to the public on GM crops. I think the FDA should take a more active role in making that information available either directly or through links, so that the general public can begin to access such recommendations.

DR. BRANDT: How accurate are those? I mean I have reviewed just recently web sites having to do with medicine. Ninety percent of the stuff that is in there is wrong.

DR. ARIAS: I can state for the record how many there are that are accurate enough, but there are web sites that do promote accurate dissemination of information on GM crops. I have no doubt there are some that are self-serving, particularly in the farm and nutritional area, there is a lot of phenomenology, but I think that certainly through the societies, the scientific societies would be a good start to link, at least link that information to information that is already being disseminated by those groups for that

very same purpose, to better educate the general public on the issue of GM crops.

So, I have noted a conspicuous absence of regulatory agency links through such sites, but I am sure the societies would be delighted to get that type of input.

DR. BUCHANAN: I am glad you mentioned that. The American Society of Plant Biologists is a major activity in educating the public. It is just one of the things that is right at the top of the agenda. I know because I was president of the society a few years ago, and it continues to put resources and effort into that arena, what you consider is very, very important.

DR. BRANDT: Everybody suddenly went quiet.

DR. BUSTA: I think that with all of the communication, an item that was publicized yesterday and brought up today, as well, is that communication should not generate extensive responses and make the public more concerned about allergens than they are, and actually exist.

If a lot of the public feels that they are allergic to food, and are not, I think that part of the education process, in addition to saying what

FDA is doing, is to alert the public to the actual incidence, and not cause a major response beyond what is necessary. Maybe the allergen societies could do that.

DR. BRANDT: Dr. Maryanski, have you got all the advice you can handle or you want more?

DR. MARYANSKI: I think you have a lot of good ideas.

DR. BRANDT: What we can do, all of you have ordered your lunch. Perhaps after lunch, over lunch, some of you may have other ideas, we can get them discussed, and then we can all go home.

DR. KAPUSCINSKI: I was wondering, since we have a little bit of time, if we could maybe get a little more detail from Dr. Maryanski about exactly how we are going to proceed in the next step. For example, yesterday, there was some mention that the agency would like now to try to develop draft guidance and then run the draft by the committee.

I am wondering how is that going to actually happen, are we going to reconvene as a committee, meet face to face and discuss the draft or are we going to each receive it individually and be asked to sent in comments? Is there any general

idea of when the next meeting might be and things like that?

DR. MARYANSKI: It is a good question and I think it actually gives me an opportunity to give you a sense of what our expectation is. This whole idea of the subcommittee, did we actually explain to you that this is one of actually six subcommittees that we are forming?

DR. KAPUSCINSKI: No.

DR. MARYANSKI: Then, let me back up since we have a few minutes.

DR. KAPUSCINSKI: A little more context would help.

DR. MARYANSKI: We have had for a number of years a standing Food Advisory Committee, which is the full committee. This is now a subcommittee. Dr. Brandt in the past has been chairman--

DR. BRANDT: Eight long years.

DR. MARYANSKI: Eight long years he served, yes, and very admirably, I must say. In fact, he did manage to weave through the mine fields on the first biotech issues for us quite admirably.

But we have a Food Advisory Committee and what we have now done to give us really more

focused scientific input is to establish, I think the number is now up to six subcommittees under the Food Advisory Committee, so these are established as subcommittees of the full Food Advisory Committee, and they are all designed to look at specific topics.

This one, of course, is food biotechnology. We have other committees, one that looks at food additives, one that looks at contaminants, one that looks at dietary supplements, and there are some others that I don't off the top of my head have the complete list for you, but you get the sense that we have now a number of subcommittees under this committee.

What the goal is, is to have these committees really be essentially working committees that work on primarily scientific issues for us, so that they are focused on particular topics. Those committees, the work of those committees then would be reported back to the full committee, and in some cases, issues that are discussed in the subcommittee may also be addressed through the full committee, but basically, this is a subcommittee of the full committee.

So, our goal, once we have this up and

running, is to have probably two meetings a year of this subcommittee, so this will be a fairly ongoing process in that sense.

It does take a couple months to put together a committee meeting. It is not an easy process usually. We are hoping that the next few will be a little easier than the rest one has been, and we certainly will be looking.

We plan to look at all of the aspects of this committee meeting in terms of the logistics, and so forth, for the planning for future meetings, so this is the beginning of an experience here at the Center for Food Safety and Applied Nutrition.

We have not had these subcommittees before, and we have not been in this building before, but I think in terms of the work, I am certainly very pleased with the discussions that we have had.

Our expectations were not real high in the sense that we did not want this subcommittee to feel that we were bringing them in here to present this issue and expect you to give us some definitive answers about how to assess allergenicity, for example. That would not have been fair to you, it would not have been a proper

expectation for us.

But we think this is a good start. You now know a little more about who we are, and I would encourage you, if you feel that there are other aspects of what we do as FDA, that would be helpful to you in doing your work, that you let us know that, because we have been listening over the past two days for things that might be helpful to you in terms of doing your work, thinking about that, as well outside of just the biotechnology aspect.

We want you to be able to understand what we do, what we can do, what we can't do, as well as the issues around biotechnology.

In terms of the actual work here now, we, of course, now have suggestions, probably you have things to think about as we now proceed to develop the draft guidance document. When we speak of a draft guidance document, it is a document that we have special procedures for, and we do, once a document is developed, we do put it out for public comment.

As you heard Mr. Lake say yesterday, out intention in this process, for this particular document, is to bring it back to you as a

subcommittee before we actually put it out for public comment, so you will have another chance for input on that document before we actually publish it for another round of comments from the broader public.

My expectation would be the normal process for putting together a committee is to prepare the background information ahead of the meeting and make that available to you, so that you have a chance to read that and study it before you come to the meeting.

So, my expectation would be that we would do another meeting when we do a meeting on the draft guidance once we have it, would be to make it available to the subcommittee members before the meeting, and at the same time, I believe, Margaret, we would put it on the web. How are we doing that, how are we doing background documents?

DR. COLE: I am not entirely clear on that yet.

DR. MARYANSKI: We are working out a process here with the new subcommittee, but the idea here is that the document should be available to you before you have to come in and discuss it.

DR. KAPUSCINSKI: And your impression is

that at that point, the document is public or is it something that we would have a closed meeting about?

DR. MARYANSKI: Once we give the document out to the subcommittee, it is, in fact, a public document.

DR. KAPUSCINSKI: That is what I was guessing. And then you would get our comments, you would use that to rework the draft and then publish it officially in the Federal Register for public comment?

DR. MARYANSKI: Well, the way it works is what we would do is take the comments from whatever the subcommittee provides us, we would make whatever modifications we felt were appropriate to the draft guidance.

We would then publish an announcement in the Federal Register of the availability of the draft guidance, and would then at the same time place it on the web, so it is available then for all interested parties to comment.

DR. ARIAS: Can I ask a question in regards to sort of the more global perspective of the focus of the group and ultimately how that may impact agricultural policy down the line. In

particular, I am thinking that this panel, I think works on the assumption that these guidelines are targeted towards national agricultural industries, and since agriculture is obviously an international commercial enterprise in the United States, we export, we import.

How would these guidelines affect those types of relationships and what would ultimately be expectations there in terms of the global perspective?

DR. MARYANSKI: Well, of course, we are often asked by countries about our procedures and policies, and it has been our position to, when other governments ask for advice from FDA, that we make every attempt to respond to that, and that may be sharing our guidance documents or explaining our evaluation process or whatever seems to be the need for the other government.

We are most effective in talking to other countries when we are talking to our counterparts, in other words, those officials who make decisions about the safety of foods and food ingredients. We are not effective in talking to the public, that is not our role to talk to publics in other countries or even the people primarily interested in trade.

We do provide information, and that is one of the reasons for our web site, to make sure that everyone has access, but it is very important for us to communicate with other governments, and that, of course, is the reason we work in the Codex process.

We also work in another international organization called the OECD, which is the Organization for Economic Cooperation and Development. That organization has a task force on novel foods and feeds, and Dr. Paul Mayers is the chair--well, he was the chair, I have to correct myself, up until now he has been the chair of that. Because of new responsibilities in Canada, he has stepped down from that. Dr. Kelly from Australia is the current chair of that committee.

But you probably will be hearing from us about some of the work that we are doing in that task force also. The international activities are things that I think this subcommittee probably is going to be hearing about along with other issues that we are working on internally, as well.

We actually see this as a working subcommittee. We want to be able to discuss issues with you that relate to our everyday work. The

reason I say that is that most of the time in the past, in this center, when we have used advisory committees, it has been for something that is very much in the public interest. The Flavr Savr tomato, of course, is the one that I am most familiar with, but we have had other issues that are very much in the public interest, and we will do that, too, here, but we really want to also use this opportunity to gain your suggestions about things that relate more to our everyday work, as well as these more sort of noticeable issues.

So, we are expecting a lot actually in that sense, but as I have said, if you have any suggestions about things that you think it would be useful to discuss, we would certainly be interested to hear that. We will be, of course, thinking about issues to bring for the agenda for these meetings on the basis of what we feel are the priorities at the time.

You have now gotten one of my really long-winded answers to your question.

DR. KAPUSCINSKI: Thank you.

DR. BRANDT: I have to say that scary part is that they listen to you, and also sometimes even implement things that advisory committees

recommend, so I mean it is taken serious and it is worth your time and your effort, so I would commend all of you for doing it.

Next time you meet--you have three members missing today--I presume they will be here including your chair, Dr. Archer from the great State of Florida. He is probably down there trying to get mercury out of fish, but in any event, I presume he will be here next time, and I won't be.

The reason his expectations were so low was because he knew they were running me in as a last-minute substitute, but anyway, it has been a real pleasure for me to get to meet all of you and talk to you, and I hope that your work is satisfying on this subcommittee, and so forth.

Thank you very much.

[Whereupon, at 11:20 a.m., the meeting was concluded.]