monitor, to digest, and act on. And this is potentially a huge new endeavor of significant importance that we need to organize very, very carefully to avoid being swamped by the magnitude of the information following.

Dr. McNeil: Doug, did you have a comment?

Dr. Throckmorton: Yes, I just wanted to follow-up, because it' important to understand, I think, also that the FDA cannot be the only affecter in this situation. There are -- it is -- it' not going to be possible for us to imagine inspecting in the quality to prevent all of these things from happening. I think melamine is a perfect example of that, where you know, there were other opportunities for people to identify the risks, here, and intervene. And there are other players that we need to be working with here, as well.

Dr. McNeil: Randy, I had one question regarding your first slide, where you asked about what substance, what products could be faked. And the question there is, if you had a bevy of chemists sitting in a room, would they be able to think

through what kinds of reactions and contaminants are likely to be productive in sleuthing out this product, this problem? For example, the nitrogen, the melamine and the protein content and the keldol reaction. Could somebody identify analogs to that?

Dr. Lutter: I'd like to think the answer is yes, but, you know, we haven't -- we haven't --

Dr. McNeil: You haven't come up with it?

Dr. Lutter: We don't -- we're not confident that it is. And that's partly why we're soliciting your input here.

Dr. McNeil: So, I guess the question is, are chemists, nationally, being asked to think about this in the context that you've presented to us?

Dr. Lutter: Well, we -- we'll announce a public meeting in -- very shortly. The meeting will -- we expect to occur this spring, and when we announce that, we will share that announcement publicly with everybody, including the academic community of interested chemists.

Dr. Spielberg: I suppose the thing that scares me is that the bad guys are smart.

Dr. McNeil: We can be smarter.

Dr. Spielberg: And that's it. And it reminds me very much of internet viruses, you know, I mean, what's the motivation for folks screwing up the internet by throwing out internet viruses?

Some of it's a somewhat similar mentality, but frankly I don't understand the psychology of it all. But on the internet side, obviously, smart people are now working for the good guys, to figure out how to deal with worms and viruses. And I think we're going to have to -- to some extent, as Barbara suggested -- be a little bit proactive of thinking forward about where the vulnerabilities really lie in our old assays, in USP standards and I know the USP is actively involved in thinking about that and partnering with FDA about thinking about these things. And the real risk to the whole world of excipients. That's where we're most vulnerable, and they're a fairly well-defined group of excipients, and FDA is involved in regulating those things, and USP is involved in developing standards for them. I think, you know, it's that whole area that we really

need to sit down about and think through each one of them, and where there are vulnerabilities.

Dr. McNeil: So, Randy, before calling on Alan and Jim, I wonder if one thing you might think about is the extent to which, in any way, the Science Board, or a subgroup of the Science Group Board -- depending upon individual expertise -- could be specifically helpful. You don't have to answer that now, but it might be something to think about because I'm sure that there's a lot of interest here.

So, I have Alan, Jim, and then David.

Dr. Russell: Yeah, I'm hoping that I misheard what you said when you said you were going to hold a public meeting to bring in people to comment on, and be creative about where the holes are in the system, and to identify chemistries that could be used that provide risks.

It reminds me that the U.S. Army for a long time had the patent for the synthesis for VX nerve agent, online, as an Army patent. I would just strongly encourage you never to do this in the

public eye.

There are so many threats that our nation faces, the last thing we need is a whole host of brilliant chemists coming up with terrible things that you could do, and then having the FDA talking about how to protect themselves against it. I mean, it's a great activity, but it should be done utterly away from the public eye, forever.

Dr. Broach: So, following up on both Barbara and Steven's comments, trying to anticipate thinking like a thief. I'm trying to understand exactly where you could make money, and therefore anticipate where the targets might be.

It's difficult for those of us who are not -- who are naturally honest -- and so it's very difficult to come up with those ideas, because we just don't think in that fashion. And, in fact, from that context, many of the computer firms hire hackers to try to teach them where their vulnerabilities are. Similarly, many banks hire bank robber to figure out how they can find where the security risks are.

And I always wonder if there was an equivalent in this area that we might tap into as a consultant. To be able to bring somebody in who would think in those terms, of being able to try to identify where -- if you were told your livelihood is going to come from an adulteration -- where would you go? And if people think in those terms, or they have done so in the past, may be able to provide useful information for where they might go in the future.

Dr. McNeil: A new fellow.

[Laughter.]

Dr. Parkinson: Would definitely make an interesting notice in the Federal Register, but --

[Laughter.]

Dr. Parkinson: My question really comes off Cathy's point. She alluded to pharmaceuticals, and I realize you've talked mainly about food adulteration. But it seems to me the economic drive is at least as great, and the opportunity for malfeasance is at least as great -- does a parallel kind of war gaming strategy exit on the drug side?

Maybe Doug, if you could comment?

Dr. Throckmorton: Yeah, absolutely. And it's a great point. Is it as far along as we wish it was? I think, as Randy said, I think we're always interested in help. But counterfeiting has been a place where we've had to put a lot of emphasis. And it -- it sort of feels close to adulteration, if you will, and so you can look at that world and think of things that might motivate people to counterfeit products, as the beginnings of a strategy, here.

And so, products that are used by large numbers of individuals that are very expensive. Products that are not regulated very tightly. So, dietary supplements and things like that, are places that are very attractive to put a little something extra into.

Things that are very expensive and used illicitly, sometimes, are obviously very attractive, because then there's less incentive to report. Our Office of Compliance has sort of worked through, and there's -- we have a list of 8 or 10 things that we

use to identify targets for potential counterfeiting and adulteration, and those sorts of things. Yes, much more work needs to be done, but there is that work that's gone on.

Dr. McNeil: Doug, is that something that this group should hear a little more about? This is the first time I've heard about that activity. And maybe I was asleep. But --

Dr. Throckmorton: We'd be happy to talk more about it. I think all of the Centers -- and I'd defer to Randy, but, you know, several of the Centers have done work around some of these areas. Again, there's a need for a sort of systemic -- you know, a systematic look at this, I think this -- the effort that Randy is doing is terribly important for us. And each of the Centers have been on the group, and have contributed our thinking and things. You know, I'm looking at Steve, and I know that Foods has done a lot of thinking along these lines, as well. And we'd be happy to share the thing that we could with you.

Dr. McNeil: Well, maybe you could talk

offline to see whether that is something that we could put together.

So, let's see, Rhona?

Dr. Applebaum: And this is just to echo a number of things that have been said, but, you know, after 9/11, there was a lot of work done on behalf of the food industry in terms of identifying what those vulnerabilities are. What could get the highest gain, at that point in time, looking from a fear factor, not an economic factor.

But at the end of the day you're dealing with criminal behavior, full-stop. So, I think to get the necessary experts to assist in this kind of activity and strategy is absolutely essential. And again, it gets to, you know, what's the highest vulnerability, with the lowest amount of energy input, for the highest economic gain. I mean, there's almost an equation.

But I also want to just echo what people have said. The last thing we want to do in terms of talking about this publicly, is to give a how-to to those people who have a deviant mind on what to do.

So, we just have to be real careful. We -- I know we went through this when we were looking at it from a food security perspective. And this is, again, instead of doing fear, they're just doing economics.

And then a call-out. As the economy of the world continues to plummet, people are going to be doing things that we can't imagine. And not to be the voice of fear, here, but just to say, you know, in terms of this area being absolutely critical right now.

Dr. McNeil: All right, so we will try not to prepare a primer on how to contaminate foods and drugs. We'll do that.

Let's see -- Jesse, maybe you could have the final comment? Because I think we need to move on.

Dr. Goodman: Just to reemphasize and refocus something Doug said. I think this is very clearly a shared responsibility, and in fact, you know, FDA needs to think about these things and be aware of possible trends and recognize that not all contamination will be natural, et cetera. We

certainly think about this in terms of terrorism issues, but also people -- particularly manufacturers, are responsible for their source materials and their suppliers.

And in general, just like with the public, if something is too good to be true, it probably isn't. So, it is the economic thing that drives somebody towards a supplier that really needs to be examined, as well.

Dr. McNeil: Well, this has been a terrific discussion, and I think we could probably go on a little bit longer, but I think we should move onto David Parkinson's update on his role in selecting priority areas that will benefit from the infusion of money that our friend Frank Torti, here, has found.

SUBCOMMITTEE REPORT ON FDA'S PROJECTS IN SCIENTIFIC PRIORITY AREAS, DAVID PARKINSON, M.D., SCIENCE BOARD MEMBER

Dr. Parkinson: Well, good morning. I don't think mine is going to be nearly as interesting a presentation, because I'm going to

talk about activities that have not yet occurred.

And, Carlos, if I could have that first slide, or is that supposed to -- ? Okay. I'm known for my soft voice.

As you heard from Dr. Torti earlier this morning, the FDA -- as a matter of strategy with respect to its science -- has created a list of priorities based on input from each of the Centers. And Dr. Torti has asked the committee, the Science Board, to create a subcommittee for peer review of these projects -- just for external validation. I think all of us would agree that this is a good idea.

Now, you see only my name there, we hope to be able to announce by the end of this week, the other three subcommittee members who are currently being vetted for this exercise.

Here's the charge to the subcommittee, which is to review each of the Centers' projects, and a series of quite specific scientific proposals have been submitted within each of the FDA-designated scientific priority areas. And I'll go

back to those again in a second.

The charge to the committee is to assess the quality of each proposal, as well as its relevance to the mission of the agency. You've seen this already this morning from Dr. Torti. And it was interesting that, although I guess each of the Centers was asked to develop three priority areas, in fact there was enough overlap that I think it's -- seven major priority areas have been addressed.

You've heard about one of them in some detail this morning from Dr. Acheson, the rapid detection. And I thought it would be useful -- even though Dr. Torti, I think, on a previous meeting did show these priority areas -- just to walk through them, and to describe to you the general topics raised by the Centers that you see, but I'll go through, Center by Center.

CBER identified rapid detection as very important, issues related to pathogen threats to blood and tissue supply. It also identified the development of standards, re-agents, and assays for rapid response to emerging pathogens as an important

priority. And, additionally, CBER proposed harnessing of new science for pathogen detection as we have heard about already this morning; adverse event detection analysis with enhanced analytical capability.

And then, of course, the development of biomarkers and application of genomics, as we have heard about already from Dr. Torti's presentation. The development and use of improved preclinical models was an important priority for CBER.

Going on to CDER, again, we see the theme of adverse event detection and analysis, an important one, one which has been high-profile in the public mind over the last couple of years.

Additionally, the topic of biomarkers and particularly, the focus on genetic basis for drug adverse events.

CDRH also has identified rapid detection as we've heard about this morning, particularly from the context of the safety of ophthalmic medical devices, and apparently, also with respect to new approaches to analyzing chemical contamination on

medical device services. Adverse event detection analysis, again, from the CDRH perspective.

Biomarkers from the device perspective, that is, personalized medicine diagnostics development is a very important aspect as you all recall, that CDRH regulates the development of diagnostic tests. CDRH has also identified clinical trial design and analysis amongst their high priorities.

CFSAN, as we've already heard about this morning, has talked about rapid identification of food pathogens and field trials of particular technologies. They also -- and I think this relates to a comment made by Lonnie King earlier this morning -- have identified microbial ecology, a new concept to me -- as an important upstream approach to prevention of food-borne contamination. Manufacturing science, and the whole technology of high-pressure processing has been identified by CFSAN.

The Center for Veterinary Medicine, again, has identified rapid detection. Notice the common

1 themes to some of these topics which emerge. And
2 more comment about that in a minute. They've
3 identified simultaneous detection and identification
4 of food borne bacterial pathogens -- very similar to
5 some of the other Center comments.
6 They've identified the development of
7 rapid immuno-chemical tests for the detection of
8 banned proteins, similar to some of the discussion
9 we've just finished. And then they've talked about
10 next generation regulatory mechanisms.
11 Again, adverse event detection and
12 analysis on the veterinary side is a common theme,
13 and there are some specific examples outlined on
14 these particular -- on this particular slide.
15 Veterinary medicine has also identified
16 manufacturing science, and you see those topics
17 outlined.
18 The National Center for Toxicology
19 Research, and Dr. Slikker is with us here this
20 morning, has again identified rapid detection. Has
21 pointed out the potential value of biomarkers in
22 toxicity assessment and prevention, and has

specifically raised the issue of personalized medicine interfacing with nutrition, which is a rather unique, I must say, concept in the context of what's going on in the personalized medicine world.

The Office of Regulatory Affairs, which I spent a lot of time looking at over the last year, courtesy of the last subcommittee charge, has -- of course -- identified rapid detection, and you see a lot of potential applications here, and clearly their activities span the goals of all of the other Centers, so it is no surprise, given their mission, and the spectrum of their activities, that rapid detection is important to them.

So, going back through all of these proposals -- which, I think shows you, one, the huge range of responsibilities that this agent has, and two, the very important, because it's quite easy to look at all of these topics and see their potential importance to the American health. It's very interesting that you can narrow this down into 7 broad priority areas. And it's quite interesting to see that rapid detection, and things like adverse

detection analysis and biomarkers, keep coming up again, and again.

Now, the other three subcommittee members are in the process of being appointed. We have the opportunity to review, quite rapidly, so as not to hold up the process, specific proposals around the top priority science projects, which have already been presented to the Science Commissioner's Office.

I've had the opportunity to look at those projects, I've read them in detail, I find them, personally, to be all of high quality and relevance to the Agency's mission. It will be important for the other three subcommittee members to similarly take a look at these, and I think, quite rapidly. Again, so that this external peer review represents value-added, as opposed to time delay, in the review of these extremely important issues for the Agency's mission.

For example, given what we've heard from Dr. Acheson this morning, it seems almost a truism that one would want to explore new technologies to take advantage of these technologies in improving

sensitivity, specificity, as well as timeliness of rapid detection.

It seems amazing to me that it is entirely possible that there will not be enough resource to support all of these science priority projects in the current budgetary world, but apparently that is the reality.

So, a few comments I have about my own concepts about how this subcommittee will function, and then we'll open it up for discussion. The first of it is that we will focus primarily on the seven priority areas as we've been asked to do.

We will comment upon -- but I believe it is the Agency's purview, to ultimately determine prioritization. The rapid detection examples -- we've heard a bit about that this morning, represent an interesting opportunity, and that related to my question earlier this morning, for cross-center collaboration, participation, shared technology development, critical mass establishment and even realizing that the potential applications may be quite different for this common technology in the

different settings.

So, it's quite clear that the goal of this program is to advance regulatory science, consistent with the kind of philosophy we heard about from Dr. Torti this morning, and as I see the role of this subcommittee which will exist for a finite period of time, as we learned yesterday, is the natural lifespan of subcommittees, we will nevertheless attempt to add value to, and not detract from, the mission of the Agency in terms of its improvement of its regulatory science.

With that, I'll stop and open it up for comments.

Dr. McNeil: David? David, you may have said this earlier and I missed it -- can you give us a sense of how many applications you have to review and how many you are going to actually award? Or, maybe that's a question for Frank?

Dr. Parkinson: I'm going to turn that over to Dr. Torti. I know how many I have to review, it's about 5 inches deep. With respect to how much money there is to fund those, that's Dr.

Torti's venue.

Dr. Torti: We'll know much more about the 2009 and 2010 budgets in days to weeks.

Dr. McNeil: So, no? All right, next meeting. All right.

Questions? So the timeframe for this is, what?

Dr. Parkinson: I think we expect that the committee will exist towards -- through the end of this year. The first task, of course, we'll be able to do quite quickly, which is the review of the initial pass of the priority projects submitted by the various Centers. We'll do that quite quickly.

I think there will be some opportunities -- and I, personally, would be interested in an opportunity for subcommittee members at some point to interact with Center Directors, and look -- or at least to have comments from Center Directors -- about opportunities for shared technologies. And I would look forward to that.

But as the other subcommittee members are appointed, you know, at that point we'll sit down,

we'll talk amongst ourselves, we'll interact with Dr. Torti, and Dr. McNeil, and then perhaps with the Center Directors, if that makes sense.

Any other thoughts, recommendations?

Dr. Pena: I can probably add that there will probably be some type of interim report at the main meeting, and then a follow-up report to the Science Board at the fall meeting.

Dr. Parkinson: In that case, thank you very much.

Dr. McNeil: Okay, thank you very much, David. I know everybody's looking forward to your report.

Well, why don't we move on to Norris? Oh, he's there already. Annual review of the FDA research programs.

PLAN FOR THE ANNUAL REVIEW OF FDA REEARCH PROGRAMS, NORRIS ALDERSON, PH.D., ASSOCIATE COMMISSIONER FOR SCIENCE, OFFICE OF THE COMMISSIONER

Dr. Alderson: Well, thank you. My objective this morning is to formally introduce a new initiative for the Board, and hopefully that you

-- with my comments -- will understand the importance of this to the Agency and also be willing to take this on.

So, at the end, if you don't have any questions I'll assume that's a no. If you have questions, I'll assume that, yes, you're ready to take this on, and really engage us.

So, a little history on prior reviews. If you'll -- there's a mistake the first line, I didn't correct -- 1955 to 1962, there was a Citizen's Advisory Committee that prepared a Science Report. In 1991, there was an Edward's Commission report, and I want to remind the Board, this body was formed in the mid-nineties, under Dr. Kessler. So, the things that I have on here after the mid-nineties, the Board has been involved in.

So, the first one I really want to point out to you is the Korn Report of 1997. This was a significant report on FDA's inter-mural research programs. It's probably second in standing to this Board's report of 2007.

This was not as long, it was 34 pages in

length. But Dr. Korn felt so passionate about this issue that he wrote an editorial that appeared in Science Magazine in 1997. And the title of his editorial was, "FDA Under Siege, the Public At Risk." Sound familiar?

But since that time, we've had the 2007 report, which we're all familiar with, and ongoing with those reports, there's been Center-specific reports of CDRA, CFSAN, CBER, NCTR. But there's also been very targeted science issues that Center Directors have asked for the Board's input -- the ORA pesticide program, the National Center for Tox Research, and their review, and the NARMS program, which Dr. Lonnie King was chair of.

But there was a common theme in all of those reviews, in that the Board looks to assign -- the FDA looks to the Board for advice on specific and technical issues. And that theme continues today.

Another thing that -- besides the 2007 report of the Board -- that's driving this is the Food and Drug Administration Amendments Act of 2007.

Just to refresh your memory a little bit, that Act established the position of Chief Scientist at FDA. It also laid out some specific responsibilities of the Chief Scientist.

Just a brief review -- oversee, coordinate, ensure quality and regulatory focus of the Intramural Research Program -- all of these are related to the Intramural Research Program -- track and coordinate the research. And we have it developed internally, now, by database, that is updated twice a year, on the Intramural Research Programs, that all of our scientists in the Agency can look at what is going on across the Agency.

The biggest thing Dr. Torti's been dealing with is develop and advocate a budgetary support for the programs, and indeed, he's done that. Develop a peer-review process -- and that's what we want to focus on today -- identify and solicit Intramural Research Proposals. You've heard about the Challenge Grant program. That's what that program is about. So, a lot of these things are beginning, and beginning to take place.

But I want to focus today on the development of the peer-review process for our Intramural Research Programs.

So, here are the objectives for you, as members of the Science Board, and are going to serve on these subcommittees. Science and technology are advancing. We need your input on how well are we using these technologies? How do we prioritize our research within our Centers? What's the process? How is senior management involved in the oversight of these programs?

The biggest thing is, is there impact on that research on both policy and guidance? Do we have the appropriate and available science? Communication -- we heard about that a little today on other programs, but certainly -- how do we communicate these research programs and the impact they have on our regulatory policies?

Is there infrastructure available, and the quality of that infrastructure? And, is it meeting the Center Directors' needs for their specific regulatory issues?

Center Directors also have the option on any time to come back and say, "I want the Science Board to look at a specific science area, to give some feedback on that specific area." This is beyond this intramural review.

So, here's the process, and David talked about that a little, in what he's going to be doing. But this is, we need immediately, Dr. McNeil. We need a subcommittee for CVM, and we'll come to that shortly. Subcommittee is two or more members from the Board, and we usually add some additional subject-matter experts.

We need a draft at work plan. Subcommittee collects data. There will be an interim report to the Science Board, and then a final report, which the Board will ultimately vote on and transmit to the Agency.

We want to formally institute the cycle of review over a 5-year period, starting next month will be Center for Vet Medicine -- I'll say more about that in a moment. Later this year it will be CFSAN, and then next, 2010, we'll go -- each year

doing one of the Centers.

So, those members of the Board that have just joined us, the first Center will be the Center for Vet Medicine. This gives you a brief overview of what the mission of that Center is.

More specifically, they're responsible for animal drugs, appliance-related issues, post-approval monitoring, and final animal feed safety.

You've heard a little bit about melamine, that's when this all started, with animal feed. But a significant part of that Center's responsibility is animal feed safety.

A proposed timeline for the CVM review. Notice we want to start next month, and we'll finish this up at your August Board meeting.

The second Center this year will be CFSAN, our food center. This is their mission statement. This is not an inclusive list of all of the things they're responsible for, but you need to note the wide scope of responsibilities that Steve Sundlof has. It's not just pathogens we're detecting in peanut butter right now, it goes far, far beyond

that. A proposed timeline for the CFSAN review, this will carry over to your first meeting in 2010.

So, our next step, Dr. McNeil, is -- assuming the Board wants to take this on, we hope you do -- is we will need a Subcommittee. But I want to wind up my comments with this slide, to review why this is important to the Agency.

First, we believe it's within the mission of the Science Board. The expertise and the scope of that expertise on this Board is very critical to the Agency. It provides an outside view of our programs that is so critical to us. But it focuses on our science. And I want to remind you, in my last bullet, there, that you are advisory to the Commissioner -- you are the Commissioner to the FDA's only Advisory Committee. So, your advice and counsel on issues of science -- which this certainly is -- is critical to the Agency.

I'll stop there and hopefully answer any questions you might have.

Dr. McNeil: Norris, thank you very much. I wonder if I could take the liberty of starting

with a couple of logistical questions.

So, you mentioned CVM and CFSAN as being the first two for this calendar year, which will actually -- the CFSAN one will report out, I think you said, in February.

Dr. Alderson: Correct. CVM will report in August.

Dr. McNeil: CVM in August, CFSAN in February.

Dr. Alderson: CFSAN in February.

Dr. McNeil: And presumably one, something else --

Dr. Alderson: And another one would start next -- in 2010, CDER.

Dr. McNeil: Okay, and then we also have, CDER, right. And then we also have, presumably, something to do with IT that Dr. Torti mentioned in his introductory remarks.

So, logistically, then, I see CVM, CFSAN, IT, and CDER as potentially things that will have report-outs before the middle of 2010?

Dr. Alderson: Well, the -- we didn't give

you a schedule for CDER, but it could be as late as the November meeting, depending on what schedule we want to stay on.

Dr. McNeil: But it's not, okay -- okay.

The only reason for bringing this up is, I think what I'd like to do is hear from the committee about -- or, hear from the Board -- about their thoughts regarding Norris' presentation. But if everybody seems to be on board with the kinds of evaluations that you've proposed -- and we've talked a little bit about this in the past, so my assumption is, everybody's going to think it's a go -- then what I'd like the Board Members to do is think about the various committees that are coming up, and think about which ones -- if they had their druthers -- they would prefer to be one of the two members on. That's why I was going ahead to CDER and IT.

Dr. Alderson: Right.

Dr. McNeil: So that people don't -- people's workload is spread out a little bit. Is that fair?

Dr. Alderson: Oh, yes, absolutely. I agree.

Dr. McNeil: Okay, questions for Norris? He said something like, if there are no questions it's a "no," and if there are questions, it's a "yes." So, I asked a question.

Dr. Alderson: Absolutely.

Dr. McNeil: So, that counts.

Dr. King: So, Norris, can you talk a little bit about outside members that would be part of the subcommittees and how they're vetted, and how we go about -- ?

Dr. Alderson: Excellent question, Lonnie. Obviously, we think it's important to bring outside consultants into this process. We'll work with the chair of these subcommittees. We hope you'll ask for our recommendations, as well, you don't have to accept our recommendations, but I remember on the BPA, we gave you -- the Board, a list of potential outside consultants to add to that committee. You add -- you used some of those, you brought in others. So, it's up -- in our view -- it's up to

Dr. McNeil, the Chair, and the chair of the subcommittee to work with us to get that -- to make that happen.

And, of course, you've got to go through the clearance process, too. So -- but the outside consultants, I think we all agree are very important to this issue.

Dr. Woteki: Well, this task certainly does fit squarely within what I consider to be the responsibilities of the Science Board, and also follows on directly from the recommendations of the Science Board's report. So, I think it's great to see a schedule like this, and the dedication to really go through and begin what would be a periodic review. So, I think it's a really great undertaking for this group.

On question -- is -- depending on the size of these groups, just the management of trying to, you know, schedule sessions, get people brought in, and incorporate a variety of different viewpoints into a cohesive, coherent report, can take some resources. And, to what extent would there be some

staff resources made available to support these reviews, or would it be the expectation that those responsibilities would fall on the members of this group to provide?

Dr. Alderson: In the past, Cathy, we have made resources available to help with that process, depending on the individual Subcommittee, and what it needed. And it's varied all before, with the Science Board Report 2007, we -- under contract -- had an outside person help that committee do that.

For the BPA, they wrote their draft report, we did a number of internal reviews for -- to review, factually, what was there, and gave that feedback. So, there are a number of ways to do this.

Dr. Linehan: With an eye to evaluating Centers, it's puzzling about what might be involved with this, and with -- now, so the process is that the Center does a self-study, so that there's a document available so that in addition to a mission statement, there's -- all the goals and objectives are spelled out with a self-study of how they have

been achieved, so there's some structure to work with?

Dr. Alderson: That's correct, Jack. I think CVM has a number of documents they will get the subcommittee started with. They have a plan on how they go through the prioritization each year -- it's 3-year plan, it's updated every year, they have an annual report. So, there's a number of documents that, I think, each of the Centers will be prepared to give you on how they go about managing their research programs, as well as the results of that.

Dr. McNeil: Okay, so let me make a suggestion, if I could. This is -- there's nothing binding about the following questions, but realizing that we have CVM, CFSAN, and I'm going to ask at the end of the day, your opinion about an IT subcommittee, and realizing that CDER is sometime, presumably, an appointment by the end of this year, or a recognition of the need for that. I wonder if -- and realizing that we all can't do everything -- I wonder if those of you who are interested in the CVM task force could just express your interest now?

Who knows whether you'll change your mind, or if the Agency will change its mind, or whatever. But, just -- anybody have a particular interest in -- yes, I want a show of hands.

[Show of hands.]

Dr. McNeil: Oh, so Cathy, Lonnie -- that's good. How about CFSAN?

[No response.]

Dr. McNeil: Oh, come on.

[Show of hands.]

Dr. McNeil: Rhona -- oh, John Floros who's not here. We nominate him in absentia? That'll teach him.

[Laughter.]

Dr. McNeil: You could do both?

Dr. Woteki: I could also do that, I can do one or the other, but not both.

Dr. McNeil: Okay.

Dr. Woteki: Right.

Dr. McNeil: We'll put your name down. Okay, and just -- we'll talk about IT later, but as long as we're on a roll, here, who's interested in

IT?

[Show of hands.]

Dr. McNeil: Dr. Kim? Obviously, anybody else?

[No response.]

Dr. McNeil: Okay. And then just jumping ahead, as I said, these are very preliminary, but just so that we have some idea, how about CDER?

[Show of hands.]

Dr. McNeil: Dr. Spielberg, Dr. Parkinson, Dr. Fitz -- okay, Garrett, Fred -- lots of people. Okay, that's a good start.

Anything more on that, Norris?

Dr. Alderson: That's good, thank you.

Dr. McNeil: Okay, great.

All right, that was terrific. Thank you very much for that.

Okay, should we move on to Dr. Mansfield, in absentia? And invite Dr. Torti to -- ?

Dr. Torti: So, I'm not going to go up to the podium, here, let me just very briefly go over and -- I don't even think I'll go over it with the

slides.

Dr. McNeil: They're in our packet.

Dr. Torti: Yeah, they're -- let me start out by saying, we hope she feels better and her back gets better rapidly.

I'm very aware of this issue, and it's actually an essential issue. As many of you know, you can take a micro-ray from ostensibly the same tissue, or in fact from the same tissue, and depending on how it is -- or take a tissue -- and then depending on how it's stored, in what it is stored, how long it's been exposed to room temperature, you can get a pattern of gene expression that is remarkably different, and will actually lead you down a different scientific path. That's true of RNA, of course, and it's well-known, it's also true of proteins, and it's also true -- but to a lesser extent, but to a real extent, to small molecules.

So, it is absolutely clear from an FDA regulatory standpoint, as we move toward genomic submissions, we now have voluntary genomic

submissions, for example, related to various applications before the FDA, as well as we move to evaluate new products, as we evaluate diagnostics in terms of their ability to actually -- complex diagnostics -- and their ability to reflect on patient prognosis, or outcome, et cetera; that the underlying and hidden piece of this is the quality of the material that goes into the assay. And that if you start with junk, no matter how good the assay is, you're going to get junk -- junk out.

So, it's absolutely essential that we take a look at this from a regulatory standpoint. And the process that we propose -- not surprisingly -- involves the Science Board, and involves bringing this issue to them. We want to broadly, today, begin to get your advice. We may -- God forbid -- have another subcommittee at some time in the future that will address this issue in more detail. But what Liz was planning to do was to outline a series of events that will start with our formal request for -- for information or comments from a few of the major groups that think about this everyday -- that

includes groups of pathologists who, national and international groups, who deal with tissue specimens. Obviously involves the American College of Surgeons, because the quality of a specimen is not only under the auspices of the pathologist, but also under the auspices of the surgeon, in how quickly this gets out, and is treated during the peri-operative period, and when we're talking about tissues for analysis.

So, we want to begin to get some guidance, as well as from the many other organizations that are engaged here, and then hold a public meeting where we can actually begin to formulate where we need to go in these areas, with the eventual aim of providing for our stakeholders, some guidance as to how -- what would be the best standards for tissue acquisition and manipulation for FDA submissions.

So, this is actually a task which is central to the genomics initiative -- it's often not thought of as genomics, but it's at the core of genomics, and Liz is completely engaged in the idea of tackling this.

I mean, it's a great example of the -- how science, in any way, relates to regulatory decisions, as well, in you know, you get -- you drill down to the issues of the quality of the specimen in regards to the robustness of the inference that you make. And it's a big topic, but one that we must pursue.

So, that was -- she was going to bring it -- this meeting was only just to inform you of what we're beginning to do, and to outline some of the next steps, and then to have a -- just a general discussion about this topic.

Dr. McNeil: Frank, before I open the floor for further discussion -- this, your activity here, would apply to FDA-regulated products? Or to submissions? So, if there's a home-brew lab test, what happens?

Dr. Torti: That's a more complex story than I can sort of address at this meeting. Right now we're just looking at trying to set the standards for the quality -- or just reflect on the standards that would be appropriate for the quality

of specimen that would come to the FDA for regulation. So, that's really all I can say about that.

Dr. McNeil: The reason for mentioning this a little bit, I'm going this afternoon and tomorrow to CMS, which is holding an all-day meeting as part of its coverage group, and I'm not sure if you know about this, but it might be that somebody should be there, to look at the kinds of considerations that CMS should think about in evaluating pharmacogenomic tests. And, interestingly, this whole area was briefly alluded to in the panel pre-meeting conference calls, but not with a whole lot of depth. And it might be that there should be some discussion of it there.

Okay, further -- yes?

Steve, then Cathy?

Dr. Spielberg: Just a couple of thoughts about additional collaboration. Obviously, the Human Genome Institute is important, too. But also, the NIGMS Pharmacogenomics Network. Because they are, again, engaged in validating various different

kinds of protocols at multiple different Centers where samples are, again, obtained under slightly different circumstances, stored, shipped differently.

And, you know, one of the things that sometimes happens is a discontinuity between GOP practice for FDA submissions, but then what goes on in the general community, either in doing investigate or sponsored, or NIH-sponsored studies, but then ultimately real clinical practice.

And, I think in terms of getting best practices in handling of samples and standardizations, it would be great if the Agency could work with all of the other groups who are now working towards that. And again, CMS is playing a role in this, because they're going to be paying the bills -- or not -- for certain types of tests to be done, coordinated with the labeling that comes from the agency.

Dr. McNeil: Kathy?

Dr. Woteki: Yes, is this project going to address the veterinary applications, as well as the

human ones?

Dr. Torti: What is your suggestion?

Dr. Woteki: It seemed like we've got analogous issues, so --

Dr. McNeil: Let's see, other questions? This is a big deal. This project.

Yes, Erik?

Dr. Hewlett: I take it you're talking about specimens that are at the interface between research and clinical diagnosis, so they could go either way. Plus, the potential for doing tests that we don't know yet even what they are.

Dr. Torti: I should say we've worked very closely -- there's an inter-agency oncology task force, and there are pathologists at the NIH, at the NCI, that have also been heavily engaged in thinking about this.

So, as we've conceptualized this, we've been working very closely with that group at the NCI, who had been very thoughtful about this, who has presented issues related to this, to their science -- the Board of Scientific Counselors just

recently, et cetera. So we're working hand-in-hand. This is not only an oncology issue, but certainly, to a large extent it touches very closely to oncologic issues.

Dr. McNeil: Could I ask, either you Frank, or maybe David a question?

On one of Liz's slides, she talks about the inaccuracy of HER2. Is that an issue of the sample or the eye?

Dr. Parkinson: No, it's an issue of the technology.

Dr. McNeil: It is? Okay.

Dr. Parkinson: And, you know, if you speak to the drug sponsor about what was more difficult, the development of the drug, or the development of the parallel companion diagnostic, you'll get a really clear answer.

And it raises -- in fact, I was -- I finished around 4:00 a.m. this morning, writing an article on this very subject. So, it's near to what remains of my mind.

And nothing is more important than the

integrity of the biological specimens. I don't think, to Erik's point, that we can anticipate exactly in the future what the optimal specimen is going to look like. People are happy if they get frozen tissue of some integrity. It's entirely possible, in my mind, that it may be desirable in the future to actually be interrogating viable cells, because they are so much more instructive about the pathophysiology of what's really going on. And I'm most familiar with the malignancy situation.

So, you know, the world is out there. The concept of dropping tissue into formalin, and then trying to figure out what these dead cells mean, is increasingly becoming irrelevant, to the practice sort of, targeted therapeutics development.

So, nothing is most important, the herceptin, HER2 test example is an important one of the difficulty of doing this. There has been something more than 10 years of evolution of technology in this area, from immunohistochemistry, through fish, through new PCR-related techniques, and that story is still not done.

So, it's an extremely important topic, and I really commend you, Frank, for taking it on.

Dr. McNeil: Comments or questions? Let's see, what should we do, Carlos? We should break early, is what Carlos just told me. So, I always obey.

So, let's just take a look at the schedule. There's nothing that we can change about the open public hearing, it is what it is, because it's been so advertised in the Federal Register. Which means, it will happen. We have, I think, 6 or 7 individuals who have requested to talk to us. And then we have the BPA after that. And then we'll have some brilliant comments from the Chair.

So, let's adjourn until 1:00. Thank you.

[Lunch recess 11:10 a.m.]

Dr. McNeil: I think we can probably start, the clock is about ready to strike 1:00.

Good afternoon, everyone. We have several items on our agenda this afternoon before opening the public session, which as you can see, is what is the next item on the agenda. I have a statement

I've been instructed to read, so let me start.

Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure that such transparency at the open public hearing of the Advisory Committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, the FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement, to advise the Committee of any financial relationship that you may have with any firm or any group, their products -- and, if known -- their direct competitors, that is likely to be impacted by the topic you address in your presentation.

For example, this financial information may include the payment of your travel, lodging, or other expenses in conjunction with your attendance at this meeting.

Likewise, FDA encourages you at the beginning of your statement, to advise the Committee

if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude your speaking. Is that clear?

Okay, so let us start with the open public hearing. We have seven speakers. Each individual has three minutes. We have a timer and there will be another two minutes that will be available for the Board to ask questions of the speaker.

So, the first speaker is Dr. Nancy Beck from the Physician's Committee for Responsible Medicine. Dr. Beck?

Dr. Beck: Hi, let me just adjust this, here. Sorry, I have a cold so I might sound a little funny. I don't have any financial obligations, although I'm glad you mentioned transparency because that's going to be the major focus of my comments today.

Dr. McNeil: Could you speak into the microphone?

Dr. Beck: Oh, okay.

As you said, I'm Dr. Nancy Beck and I'm a

scientific advisor with the Physician's Committee for Responsible Medicine or PCRM. As a non-profit organization, PCRM promotes preventative medicine, conducts clinical research, and encourages higher standards for ethics and effectiveness in research and medicine. I want to thank the Science Board for the opportunity to comment today, as well as for your work on BPA, particularly the subcommittee on BPA's peer review of FDA's draft assessment.

Prior to the release of their peer review report, I presented comments to the Science Board's Subcommittee on BPA, critical of the tier testing plan recommended in the FDA's draft assessment, which we felt did not place enough emphasis on the need for more accurate assessment of human exposure and risk.

Although I'm not sure what we will hear during the BPA update from FDA later this afternoon, I want to reiterate those comments. We need better exposure data and mechanistic human-based in-vitro data to address BPA, particularly in light of the mounting literature questioning our understanding of

exposure and pharmacokinetics in humans.

In addition to putting in another plug for PBPK modeling, human biomonitoring, and human epidemiological studies, I want to turn your attention to the lack of transparency and lack of stakeholder dialogue that has characterized the Agency's approach to BPA.

Since release of the strapped assessment in August 2008 and the uproar that followed, many have been anxiously awaiting an update from FDA on its plans regarding BPA. It was clear that more studies were inevitable, but it was unclear who would be deciding what studies to pursue, what those studies would be, and whether stakeholder input would be considered during that process.

I found that FDA had indeed been retooling its plans for BPA, but those plans were not readily available. The only place I could find an updated list of studies planned was in a December 3, 2008 letter from Dr. Norris Alderson, Associate Commissioner for Science, to Dr. Barbara McNeil, Chair of the Science Board.

Although this letter was not private and is in fact part of the materials for today's meeting, it is troublesome that these studies weren't announced in a more public open, public forum, and even more so that the planning of these new studies was not transparent, nor were the studies made available for comment.

The need for transparency should not be underestimated. Today, I want to ask the Science Board to encourage FDA to increase transparency and the opportunity for stakeholder engagement on BPA.

I understand that FDA must base its decisions on robust science, not on public opinion. But on an issue as heated as BPA, it's essential to get input and support from outside the agency to engender confidence in the process and the data that results.

FDA met with many factions and users of BPA at the end of January for a mutual update, and it would be refreshing to see FDA engage other stakeholders in addition to industry in such a manner. Perhaps FDA could sponsor a workshop that

included diverse experts and stake holders with the goal of reaching consensus on what studies are of highest priority and how to coordinate the research effort moving forward. Lessons learned from such an exercise may well serve as a model for approaching assessment of other potential endocrine disrupters in the future.

Thank you.

Dr. McNeil: Thank you very much, Dr. Beck.

Does anyone have a question for Dr. Beck?

[No response.]

Dr. McNeil: Okay, thank you.

We'll move on to Dr. Diana Zuckerman, who is National Research Center -- represents the National Research Center for Women and Families. Is Dr. Zuckerman -- there she is.

Ms. Brandel France de Bravo: Hi, I'm not Dr. Zuckerman.

Dr. McNeil: Could you say that a little more clearly for the record?

Ms. Brandel France de Bravo: It's Brandel

France de Bravo, probably the longest name you'll have here today. I'm here to present the statement for Dr. Diana Zuckerman of the National Research Center for Women and Families.

I'm going to skip her credentials and cut to the chase. Neither of us has any conflicts of interests.

We're very pleased with the Science Board's criticisms of the FDA draft report on BPA and we were disappointed that the FDA has not acknowledged the bottom-line criticism, that the FDA drew conclusions about the safety of BPA that were not based on sound science and that no conclusions can be made about safety until the FDA pays attention to the best studies conducted by federally funded scientists and designs appropriate follow-up research, with an emphasis on appropriate.

First I want to talk about prenatal exposures. This is something the Science Board also addressed, but hasn't been addressed sufficiently. The FDA says that they agreed with the Science Board that they should focus on the health affects of BPA

on infants and young children. However, in our testimony in October and in the Science Board's response, it was pointed out that prenatal exposures are probably even more important.

Unfortunately, pregnant women don't have a special diet of canned foods and beverages, they eat the same food as everyone else. That means the FDA needs to be concerned about BPA exposure from all containers for foods and beverages commonly consumed by adults.

Secondly, there's the question of chemotherapy patients. A study published in Environmental Health Perspectives in October and a new study published in the same journal this month, found that the effectiveness of chemotherapy for women with breast cancer could be undermined by exposure to BPA. At the Science Board meeting October, the need to study the impact of BPA on chemotherapy was also mentioned. Again, this means that BPA levels in all foods and beverages consumed by all adults will need to be examined.

Thirdly, I'd like to talk about Spragg-

Dolly rats. The FDA is proposing new research using Spragg-Dolly rats. The use of these rats was criticized at the Science Board's subcommittee meeting because they're inappropriate for use in BPA research. They're less sensitive to estrogens than other types of rats. If the FDA's goal is to do objective research, these are not the right rats to use.

So what else is needed? We're pleased that the FDA plans to do a new study of BPA levels in cans of infant formula. This decision responds to criticisms we made in September, echoed by the Science Board subcommittee on BPA, that the safety levels for infant formula were based on inadequate sample, the sample of infant formula that was outdated, too small, and not generalizable to a national sample.

So, the next question is, will the FDA move quickly to answer these crucial safety questions or will they follow the time-honored Washington tradition of study and stall? The FDA has not given a timeline for the completion of any

of the newly proposed research. The new studies will be enlightening, but the FDA has thus far ignored many very well-designed studies, which indicate that there are real risks to BPA exposure.

While the FDA studies and stalls, new research is emerging almost every month. These studies need to be scientifically summarized by the FDA to determine BPA's likely risks to human health.

There are alternatives already available to BPA, we've seen this in other countries, Japan and elsewhere, and other countries are moving to limit BPA in food and beverage contact applications. We urge the FDA to quickly do the same.

I want to thank you for inviting us hear to make this public testimony and we look forward to hearing what else has to be said.

Thank you.

Dr. McNeil: Well, thank you very much. We note that Dr. Filbert who is in charge of the BPA panel is ill in Los Angeles. He planned to come and became sick and is unable to be here, but he will be made aware of all of the comments. And of course

the FDA staff is here as well.

But are there any other questions from the members of the Science Board?

[No response.]

Dr. McNeil: And Garrett, of course, was on that committee as well.

Okay, thank you.

Ms. Brandel France de Bravo: Thank you.

Dr. McNeil: How about Dr. Rangan from Consumer Reports?

Dr. Rangan: Good afternoon. My name is Urvashi Rangan, I'm an environmental health scientist with Consumer Reports, our parent organization is Consumers Union. We're a non-profit organization and we have no financial relationships to BPA.

We at Consumer's Union appreciate the FDA's acknowledgement of BPA -- of the health effects of BPA -- and the concerns with it in their December 2008 statement. The 10-mile high view is that the change in concern by the FDA over the last few years has been very slow. Where the FDA seems

to be now is quite different from the position from where you were a year ago or two years ago. But it only seems to just be coming inline with what the public sentiment and the science is out there.

And for those reasons, the public is losing confidence in whether the FDA is really up to the task of really protecting public health, in light of all of these compelling studies that continue to come out.

I'm here to register our continued concern with the health effects of BPA and really what we perceive to be an inaction at this point to protect and mitigate those exposures and people. I want to reiterate our concerns that the levels that seem to be circulating in people's blood, of BPA, approximate those levels that are causing health effects in animals. For that reason alone, the margin of safety, the safety margins, the safety buffers are not there in this particular chemical, and therefore we believe that you, the FDA, do need to step up to the plate now and take action to create those safety buffers.

In our opinion, that means that consumers should not be exposed to BPA through food contact substances and that we think that that action needs to be taken now.

Going forward with the testing and your further evaluation, we would hope that in the spirit of transparency that those testing results are made public. Based on some of the problems with the melamine testing in infant formula, we're concerned that we're not going to see those results as you obtain those results. And so, we urge you, please, to make those results public as you find them.

We also strongly urge you, while we know you have said that you are going to consider including other studies, there are hundreds of other studies for you to consider in your assessment of BPA at this time. And that while you're continuing to study the problem, you have enough evidence out there to take action, to protect public health now.

We also want to urge the FDA to work closely with the Center for Disease Control in the biomonitoring data of BPA circulating in people.

The N. Haines data is collected every year and there shouldn't be any reason why this Agency can not work more closely with the CDC and inform the public of what the continuing exposure levels are over time.

Thank you.

Dr. McNeil: Thank you very much.

Questions?

[No response.]

Dr. McNeil: Okay.

Let's see, Dr. Anila Jacob from the Environmental Working Group?

Dr. Jacob: Good afternoon, I'm Dr. Anila Jacob, a medical doctor and senior scientist at the Environmental Working Group, a non-profit research and advocacy organization. Thank you for the opportunity to present these comments to the FDA Science Board on the issue of BPA.

The Science Board determined in its October 31st, 2008 meeting that FDA could not substantiate that current BPA exposures in food are safe. We applaud the Board's strong statement and its focus on children. We call for you to press FDA

to take decisive action to reduce exposures from FDA-regulated products.

Since the October meeting, we've seen more sobering reports about infant exposures to BPA. A study of premature hospitalized infants, led by a scientist from the CDC, found the median exposure level of the preemies was 10 times higher than that of adults. One preemie had a total urinary BPA concentration of 946 micrograms per liter. This is 256 times greater than levels in older children who were tested by the CDC.

These findings suggest that plastic medical devices are introducing BPA directly into the blood stream of vulnerable newborns. Five other new studies show that BPA alters body metabolism and causes epigenetic changes. These studies confirm BPA's developmental toxicity.

A recent pharmacokinetic model predicts that newborns exposed to the same amount of BPA as adults would have 11 times the level of BPA in their blood compared to adults, because newborns are less able to detoxify and excrete the chemical. Yet, FDA

offers little reassurance that it will quickly address the issue of BPA-based food packaging.

On December 3, 2008, the agency told the Science Board that it would reanalyze existing studies, collect additional biomonitoring data, and conduct other studies to clarify the magnitude of early life susceptibility. These endeavors should not distract the agency from pursuing its core mission, which is to protect the public health.

Today's children, as well as the 4 million babies born each year in the U.S., are being exposed to BPA at levels that may pose serious health concerns later in their lives. We don't know everything there is to know about BPA, but we know enough. With every new study, we learn more about the negative impacts of BPA on the human body, especially when it's developing. We have only one chance to protect our children. BPA exposure levels must be reduced immediately, without waiting for more years or decades of study.

The Science Board deemed that the Agency had wrongly relied on insensitive studies to

determine safety, excluding dozens of other studies finding harm at lower levels. The Agency has dug in on this point. This shows that the agency is still ignoring the Science Board recommendations and the growing consensus is hazardous at low levels.

In contrast to the FDA, the Canadian government's actions on BPA have been swift and decisive. Last fall, Health Canada pledged that BPA contamination in formula should be as low as reasonably achievable. It banned BPA containing baby bottles and carefully surveyed BPA levels in powered and liquid formula, detecting BPA in every liquid formula sold in metal cans.

The Science Board should demand that FDA set a standard for BPA in food and formula that, like Canada's actions, minimizes BPA contamination. FDA must advise parents that BPA-free alternatives are already widely available. We do not believe that insisting that formula makers use BPA-free cans will cause a major a disruption in the infant formula market.

In closing, we look for the Science Board

to remain vigilant on this critical public health issue. The Board must press for measurable improvements in the packaging of infant formula and set firm deadlines for a phase-out of epoxy-lined metal formula cans. FDA must move quickly to incorporate new studies and perform a valid assessment of health risks.

Thank you.

Dr. McNeil: Thank you, Dr. Jacob.

Comments, questions?

[No response.]

Dr. McNeil: Okay, we'll move on to Ms. Weddig from the National Fisheries Institute.

Ms. Weddig: Good afternoon. Thank you for the opportunity to address the issue of economically motivated adulteration.

I'm Lisa Weddig, I'm employed as the Director of Regulatory and Technical Affairs with the National Fisheries Institute, a trade organization representing all aspects of the seafood industry. Among our missions are ensuring that consumers have the facts on the health benefits of

fish and shellfish and maintaining consumer confidence in the seafood products they purchase, by protecting the economic integrity of those products.

I serve two roles at NFI. I provide the liaison between our members and the regulatory agencies. In addition, I serve as the Secretary of the Better Seafood Bureau, an organization separate from NFI, started by our members to provide a mechanism for our partners in the supply chain to report suppliers suspected of committing economic fraud. All NFI member have pledged to abide fair and lawful business practices, with respect to economic integrity issues, correct net weights and correct species to name a few.

In preparing my comments for today, I reviewed the transcript of your October 31st meeting. I wanted to see what had been said about the work of FDA's task force on economically motivated adulteration of foods. I was very much surprised to see that NFI was mentioned in the transcripts.

At that meeting, Dr. Sundlof mentioned

NFI's concerns with the rampant problem of economic fraud in the seafood industry, in particular, adulterating the product by adding ice or glaze to increase the weight of the product. While fraudulently adding weight to the product with excess water is not a public health risk, we firmly believe in fixing broken windows. Enforcement needs to focus on all violations of the Federal Food, Drug, and Cosmetic Act, even those that don't pose a public health risk.

Fraud prevention is a partnership between the government and the industry. Industry follows the rules and government needs to enforce the rules. But it is apparent, that the rules aren't being enforced. In fact, in the Import Seafood Products Compliance Program from FDA, it states that with shrinking resource base, economic works is viewed as a low priority by CFSAN and no resources have been allocated for this work in the field. This is just an open invitation for cheaters.

I found Dr. Lutter's presentation this morning very encouraging. NFI's members already

have one answer to the challenge of how FDA can anticipate future adulteration, identify the bad actors on other issues. We have no doubt that companies willing to cheat in one area, such as economic fraud, will also be willing to cheat or take shortcuts on food safety controls. We get evidence every day by emails from our members of companies offering products at less than 100 percent net weight.

Just last Friday, FDA reissued a letter from 1991, outlying the Agency's policy on the fraudulent practice of including glaze as part of the net weight of frozen seafood. That document reaffirmed that this practice in product that is adulterated by terms defined in the Federal Food, Drug, and Cosmetic Act, and any violation is considered a felony because the intent of the practice is to defraud or to mislead. This is a strong message to cheaters that those who illegally label products will be prosecuted.

We believe that cheaters cheat either because they are ignorant of the rules or that they

know that they can get away with it. Our members are doing what they can to cure the ignorance. Believe me when I tell that that document is going to be the most widely distributed FDA guidance document, to date. But it is up to FDA to put the teeth behind the rules and enforce. The very nature of FDA enforcing fraudulent practices, even those that aren't public health related, will hinder more serious violations.

Thank you for your consideration.

Dr. McNeil: Thank you very much.

Comments, questions?

[No response.]

Ms. Weddig: Thank you.

Dr. McNeil: Okay. So we'll move to Dr. Hentges from the Polycarbonate BPA Global Group.

Dr. Hentges: Thank you, I'm Dr. Steve Hentges with the Polycarbonate BPA Global Group at the American Chemistry Council. This afternoon FDA staff will outline for you a number of research and information gathering activities on Bisphenol A, things that are responsive to the comments and

recommendations that came from the Science Board. So I thought I'd take the opportunity this afternoon just to spend a few minutes outlining a few of our complimentary research and information gathering activities on Bisphenol A.

In general, over the years, our approach has been to identify key uncertainties and scientific questions and then look for opportunities where we can sponsor research to help address those uncertainties and questions. We've been very active sponsoring research on Bisphenol A for quite a few years now and we do have other research underway or planned.

One key question that we've been monitoring for a number of years now is the potential for Bisphenol A to cause developmental neurotoxicity. The existing literature in that area, as has been reported in other evaluations, is highly uncertain. Work that we have underway right now, we're conducting a guideline DNT, developmental neurotoxicity study, that's a study that's conducted under OEC guideline number 426 in good laboratory

practices. The study is well underway, we actually started this -- started planning it quite a while ago and started conducting it last year. The study -- the in-life phase of the study ended in November of last year and we expect the final technical report -- we hope it will be available late this year. We'll provide that to FDA as soon as it becomes available, and then, of course, the study will be published in the peer-reviewed scientific literature, which is our standard practice.

A second area of interest is the ability of infants and children to metabolize Bisphenol A. It's, I think, generally accepted that adults have the capability and ample capacity to metabolize BPA to biologically inactive metabolites. That's been demonstrated in quite a few laboratory animal studies, as well as at least four human volunteer studies.

But the capability for neonates to metabolize, whether human or animal, is not as well characterized, there are a number of laboratory animal studies that indicate that neonates do have

the capability to metabolize BPA, but it is a controversial area, there is uncertainty in that area.

However, I note that a study -- it was mentioned by one of the earlier speakers -- but a study published a few months ago on premature human infants, did show that even premature infants have quite a bit of capability to metabolize BPA.

So what we have underway, actually not underway yet, but what we're designing right now, is a metabolism and pharmacokinetics study on neonatal mice -- we're designing it now so we haven't actually got that work underway, but we hope to complete that study, or conduct it and complete it in 2009. And as with the study I just mentioned, we'll provide the technical report to FDA as soon as it's available and then go ahead and publish that in the peer-reviewed scientific literature.

We also have some activities underway that are relevant to the exposure side of the safety assessment. You heard from Dr. Beck earlier that exposure is a very important part of the assessment.

Somebody mentioned biomonitoring earlier and there's quite a bit of urinary biomonitoring data that's available right now that confirms that human exposure to Bisphenol A is extremely low. In particular, most notably the CDC N. Haines data demonstrates that point for the U.S. population age six and above.

The data from CDC is quite consistent with studies that have been conducted elsewhere in the U.S. and around the world. Those studies do confirm that Bisphenol A is excreted in the form of metabolites. And from the CDC data, the estimated daily intake is quite low, it's about 50 nanograms per kilogram per day.

There is, however, less blood biomonitoring data, much smaller scale studies, the data is highly inconsistent, it's also to interpret because of the -- because of study design limitations, and it's also not clear that the analytical methods used in those studies have been fully validated. There's also potential problems with cross-contaminations and that also leads to

some uncertainties in interpreting those study results.

So what we have underway right now, well underway, is a project to develop a fully validated analytical method for measuring Bisphenol A and its metabolites in both human urine and human blood. And once that study is -- once that method is fully validated, it will be available then for conduct of biomonitoring studies to try to get more reliable data on levels of Bisphenol A in human blood.

And then finally, FDA safety assessment shows that the primary sources of exposure to Bisphenol A for human infants and children, infants in particular, is baby bottles, polycarbonate baby bottles and canned infant formula. And while polycarbonate bottles have been a large part of the baby bottle market in the past, we're well aware that other bottles, alternative bottles are now quite prominent in the market. Many more of them are available now and we're aware that the major manufactures of polycarbonate baby bottles now all have alternatives available as well.

We're also aware that a number of retailers have discontinued the sale of polycarbonate baby bottles. All of this leads to the --

Dr. McNeil: Are you wrapping up?

Dr. Hentges: Yes, 30 seconds.

Dr. McNeil: A little bit less. Sorry, we have to be fair.

Dr. Hentges: All of this leads to the conclusion that polycarbonate baby bottles are much less prominent in the market today than they had been in the past and what we're working on now is to try to pin that down to get better data for use in the FDA exposure assessment for baby bottles.

Thank you.

Dr. McNeil: Thank you.

I'm sorry, we don't have any time for questions, so we'll move on to Mr. Robert Weiss from Hooper and Weiss.

Mr. Weiss: My name is Robert Weiss and in March of 2007 my firm filed a first class action case against the baby bottle manufacturers, so my

financial relationship to disclose is that I'm suing these guys.

At the time, there were hundreds of independent peer-reviewed scientific studies that demonstrated a wide range of adverse effects, to laboratory animals as a result of low dose exposure to BPA. Nearly two years later, scores of additional studies have been published, which further confirms a very real increased risk, not only to humans in the general populations, but specifically to infants and children who are especially vulnerable to the effects of exposure to BPA.

For decades the chemical industry has continued to misrepresent basic BPA chemistry, that polycarbonate plastic is heat resistant, which is something that they market. Therefore any level of leaching of BPA is minimal at best, which poses no risk of harm to infants and children.

This is a gross misrepresentation. This is understood, and this was told to me by the experts in the litigation, any first-year chemistry

student, if you show them BPA and you ask them this question, "What happens when you heat it?" will be able to answer that question. Polycarbonate is not heat resistant, so when a plastic baby bottle is made with BPA, and it's heated in a microwave oven to heat up a baby's formula, BPA molecules leach into the bottle's content and exposes the infants to dangerous levels of a known reproductive and developmental toxin.

Moreover, is BPA mimics the estrogen hormone. Exposure to BPA, even in a parts per trillion range -- and of course the exposure is much greater than that -- can cause a disruption to the endocrine system in the early stages of a child's development, resulting in permanent and devastating change to the cells and tissues, which is ultimately expressed as irreparable injury and disorder to the child's mind and body.

In a recent study published just last month, on January 28, 2009, in Environmental Health Perspectives, researchers concluded that BPA levels in humans did not metabolize as quickly as

previously thought, suggesting either substantial non-food exposure of BPA or accumulation of BPA in body tissues such as fat, or both. Researchers also concluded that when BPA exposure was identical between infants and adults, the amount in a baby's blood is 11 times higher, that's 11 times in the blood, and you can do your own calculations as far body weight.

What does this mean for infants and children? Low-dose exposure to BPA from sources such as baby bottles and toddler sippy cups can produce catastrophic injury forever altering their developmental -- their development as normal children -- precluding them from ever reaching their God-given potential in a world that demands the best brightest to cope with an increasingly dangerous and uncertain world. To be handicapped and restricted from realizing an infants potential is a crime against humanity, which should be not allowed to flourish for the sake of corporate profits.

I respectfully demand, on behalf of parents and families across the country, that the

FDA take immediate action to regulate BPA. Baby bottle manufactures must be required to immediately remove and recall all baby bottles, toddler training cups, and other infant products containing BPAs.

Infants and young children of America continue to be subjected to toxic level of BPA. We can not wait. Any delay in action will inevitably result in injuries to our children and future generations. We will be doomed to repeat the heartbreak and widespread loss of life seen in recent past, after physicians believed it to be a good idea to prescribe DES, which as many of you know -- BPA was marketed originally as a competitive product of DES. And my law firm continues to this day to receive inquiries from the grandchildren, the granddaughters and the grandsons -- we don't take the grandsons' cases, but we're looking at the granddaughters cases -- the grandchildren of the women who took BPA are looking for lawyers for reproductive cancers and all sorts of problems with DES.

The FDA must take action now. I come from

a tradition that you can come down into this world, into a body and suffer for 70 or 80 years, just to one favor for one person. How much more so a favor for many people? How much more so for a favor for many children? You people are sitting here in a position where you can save 4 million children a year from exposure to what we -- the evidence in my opinion -- is a dangerous thing. If it's even close, you take it away from the baby. And this is way more than close.

So, I bless you that God gives you the wisdom to see the truth and the power to stand up to the forces against and do the right thing.

Thank you.

Dr. McNeil: Thank you very much, Mr. Weiss.

Again, we have no time for questions for your presentation, either.

Are there others in the audience who would like to say a word or two or three?

[No response.]

Dr. McNeil: Well let's see, we had seven

speakers and six of them spoke about BPA, so I guess it's appropriate that we move onto to BPA, and hear from Jonathan Bernstein first.

Dr. Cheeseman: Can you folks hear me? Okay, that looks good.

Good afternoon, my name is Mitchell Cheeseman, I'm the Deputy Director of the Office Food Additive Safety, which is the unit in FDA that's primarily responsible for ensuring the safety of food ingredients and food packaging components. I want to thank you for the opportunity to speak today and provide you with an update on our activities regarding the reassessment and safety of Bisphenol A used in food contact applications.

Okay, a little bit more activity was added to this slide than I anticipated, so I'm going to click through it.

I want to start by emphasizing the fact that reassessing safety of any ingredient added to food directly or indirectly is a multi-step process. And I want to emphasize, that in many ways the reassessment that we're undergoing right now is no

different than similar activities that go on at FDA on a continuing basis. Because the safety assessment of any given FDA product is a decision made at a single point in time, FDA must continue to monitor new develops and new information for such products in order to accomplish its public health mission.

At each step, the Agency must consider the results of that review and judge how to proceed. In such cases as this one, where there's significant scientific disagreement regarding the interpretation of the applicability of the data, we will consult with bodies such as yourself to provide input and scientific expertise to supplement our review. We must consider that input along with other relevant data to reach completion of our reviews and in reaching a decision regarding the issue at hand and regarding how the issue will ultimately affect our safety assessment process.

In this regard, it's the role of the FDA reviewers, in completing their reviews, to objectively assess the relevance and meaning of the

available safety data, in relation to an established standard of safety, and the role of FDA leadership to objectively apply the results of those reviews and act to ensure that the legal standard of safety continues to be met. This process, which began for Bisphenol A in early 2007, before the completion of the NTP reviews, was accelerated in 2008, as a result of the NTP hazard assessments. I believe that this update will demonstrate that we've made significant progress since then, but that we also have a great deal to do.

The FDA Science Board comments on the draft assessment fell into a wide range of areas. First, you requested that we expand and update the exposure assessment, including developing a more robust data sampling and considering more thoroughly the assumptions and uncertainties underlying our original exposure assessment. In addition, you requested that we consider dose modeling in developing a point of departure to establish the margin of safety for BPA. You requested, or rather suggested, that the assessment would benefit from a

greater discussion, clarifying how our uncertainty factors are derived and used.

You asked us specifically to reevaluate toxicity studies deemed adequate by the CERHR panel. You asked us also to consider the value of meta-analysis in providing -- in determining the value of disparate types of toxicity available on Bisphenol A. And you asked us to expand our discussion of biomonitoring data, in particular in relation to our exposure assessment. And finally, although there was general support for our initial approach at doing PBPK testing to better understand the metabolism of Bisphenol A in animals and in humans, you advised us to consider carefully planned toxicological studies to ensure that they may best clarify the remaining uncertainties.

I won't be talking about all of those issues today, although we are working diligently on all of them. Today I will be talking just about the first three items on the slide.

First of all, I'll discuss two aspects of our update of our toxicological assessment,

specifically the use of dose modeling to derive a point of departure for our safety assessment. And I will address how we expect to clarify our discussion of uncertainty factors using the toxicological assessment. I'll go into some detail updating our exposure assessment, particular in relation to infant exposure, discussing a new exposure assessment model that doesn't rely on point estimates, and discuss development of data to assess uncertainties and parameters used for the exposure assessment. And finally, I'll discuss the many ongoing activities in relation to Bisphenol A.

Starting with the point of departure analysis, you may recall that the -- our draft assessment based our point of departure on no effect levels in the Tyl studies. And the Science Board suggested that rather than an uncertainty factor and no effect level approach, a benchmark dose analysis might leverage the dose response information in those studies more thoroughly and provide a different point of departure.

As an initial response to this suggestion,

we've reviewed the literature available on benchmark dosing analysis, specifically in relation to the Tyl studies, and there are three main studies published. The first is by the Japanese National Institute of Advanced Industrial Science and Technology, which unfortunately is a study that has limited detail, but outlines a BMDL of 23 milligrams per kilogram body weight per day in mice.

In addition, Willhite et al, in 2008, published a analysis of several more in-points in both mice and rats, and put forward a BMDL of 75 milligrams per kilogram body weight per day for female mice. The most thorough evaluation was done by the CERHR panel itself, which analyzed several dozen endpoints and arrived at two low benchmark dose levels of 35 milligram per kilogram per day in rats and 12 milligram per kilogram per day in mice. These values, as points of departure, compare with our point of departure of 5 milligrams per kilogram body weight per day, the no-effect level in mice.

Just to sum up the results to date, and this analysis is not complete, thus far the BMDL

approach doesn't indicate a more protective part of departure than FDA previously developed using no-effect levels. However, the analysis and conclusions are, at this point, limited to the endpoints examined in the Tyl, et al, study. We are considering the value of BMDL with regard to other endpoints and other data.

Moving on to uncertainty factors -- the draft assessment used a -- derived a margin of safety developed from no-effect levels using specific uncertainty factors for systemic reproductive and developmental toxicity. The Science Board suggested a more thorough description of the uncertainty factors would be a benefit to the overall assessment. We expect to address this suggestion with a revised discussion in the final update for the risk assessment.

For repeated dose systemic toxicity, we'll talk about four variables related to uncertainty. The first is intra-species variability or variability within the human population. The second is interspecies variability or the ability to

extrapolate from animals to humans. And the third is related to duration and extrapolation of the length of animal toxicity testing to chronic toxicity in humans.

These first three variables are typically -- range up to a value of 10 and did attain a value of 10 in our draft assessment. They're combined by multiplication netting an uncertainty factor of 1000. The fourth variable is based on the availability of multispecies data, and in the case of Bisphenol A, there are in fact data available in multiple species. That uncertainty factor in that situation is one.

For developmental and reproductive toxicity the situation is slightly different. We take into consideration whether or not permanent or irreversible changes that in fact may be life threatening are observed in the study, or whether the effects observed are all non-permanent, reversible changes. In the former case, we utilize the 10-fold intra-species variability and the 10-fold interspecies variability, as in systemic

toxicity, but we add another 10-fold uncertainty factor for a total of 1000. And we don't add that additional uncertainty factor for non-permanent, reversible changes. Again, there will be a much more thorough discussion of these factors in the final, updated assessment.

Moving on to the exposure assessment update -- one thing we've done is to develop a new exposure model that is not based on point distributions, or excuse me, on point estimates, but based rather on distributions of both BPA concentration in infant formula in this case and infant consumption of formula. However, to develop this model in parallel with the development of a more robust database on concentrations of Bisphenol A in infant products, we've utilized the existing data from FDA, Health Canada, and the Environmental Working Group on infant formula concentrates. This gives us a total of 36 liquid samples representative of the U.S. market for infant formula. Five, if you can count, five from this list were omitted because they're European products and we can't verify that

they're representative of the U.S. market.

The range of values for these 36 samples is .04 to 8.6 micrograms per kilogram of food or infant formula. And I want to specify here that these are at-use concentrations. These sorts of numbers are -- get thrown about in public discussions without complete context. I want to point out that the FDA numbers are .1 to 13.2 micrograms per kilogram food. The Health Canada are 2.3 to 10.2. And the Environmental Working Group are non-detect to 17 micrograms per kilograms per food. All those values are in concentrates, they have been adjusted to at use concentrations, and so you will see a disconnect between these upper numbers and the lower number. I'll be talking about at-use concentrations for the rest of the discussion.

For formula consumption, we've used the USDA Continuing Survey of Food Intakes by Individual, CSFII, which uses a two-day survey and includes data on approximately 1200 infants, age zero to twelve months.

For our probabilistic exposure estimate model, we've used distribution and place of point estimates, including distribution of infant formula consumption, which is typically logged normal, and a distribution of fit to the data on BPA concentration in infant formula, which was determined experimentally. These distributions have been sampled by a Monte Carlo process and intake calculations performed in multiple iterations. This gives us an intake distribution, excuse me, a probabilistic distribution of intakes, which is shown on this slide. The mean value that we estimate from this distribution is .4 micrograms per kilogram body weight per day and the 90th percentile is .8 micrograms per kilogram body weight per day.

Just to summarize the results and also to discuss the assumptions underlying the model. One assumption of course, is that the two-day average intake data reflects usual intake by the infants. And of course, that the analytical BPA concentration data set is representative of all infant formula.

With regard to this latter assumption,

we're developing new infant formula data. We've engaged in a robust analysis of several infant formula brands and products as a product of formula type, container size, geographic location, and storage time, many of the parameters that our initial range of data were criticized for last year.

Our infant formula sampling plan includes samples from all major brands, milk and soy products, ready-to-feed, concentrate, and powder formulations, containers of various sizes and types, and based on what we know about the infant formula market, we have focused on samples from a major East Coast and major West Coast market, because that is essentially how the -- it's based on how the infant formula is distributed within the U.S. We've also focused on collecting several cans within lots and across different lots of the same product in order to be able to discuss that variability in our final assessment.

We've also updated our method because the 1997 method, previously published by FDA, did not lend itself to rapid analysis. We've updated and

modified the method to allow for more rapid sample and incorporated a modern tandem mass spec detection approach and a modified sample preparation. We've completed in-house validation with spike samples and we have some initial analytical results.

The recent results within the past week on 57 samples show a ranges of .02 to 10.55 micrograms per kilogram of food or infant formula, which are comparable to the existing data and also show, at this time, again, initial results, no statistically significant geographic variation. I can't speak to the other variation that we will be testing for, yet.

You also suggested that we reexamine assumptions made, particularly with regard to BPA migration from polycarbonate bottles into infant formula, in the initial draft assessment. To do that, we've looked at studies BPA migrating from polycarbonate into formula, migrating to infant formula specifically from microwave heating, or resulting from excessive dishwasher use of polycarbonate -- for polycarbonate bottles, that is,

and also BPA migration from polycarbonate bottles, based on terminal sterilization. We're looking at the impact of brand loyalty on exposure and the impact of the use of powder versus liquid concentrate formula.

An important aspect of this reexamination is utilizing data from the infant feeding practices study, part two, which is a collaborative study by FDA and CDC, conducted between 2005 and 2007, including over 2000 infants, including participants from the Women and Infants and Children program, to provide infant formula to low income mothers. Questions in this study include the subjects of formula purchased, label reading, mixing, handling, and other practices.

And I'm going to give you a snapshot of the questions that we think may be most relevant from this study, not a complete picture of the data in this study. First question, do you heat the bottle in a microwave oven? Sixty-five percent of all mothers report that they rarely or never heat bottles in the microwave oven, over all ages.

Eighty-five percent of WIC mothers report rarely or never heating bottles in microwave ovens.

Do you boil water for formula? Most mothers did not boil tap or bottled water used to reconstitute formula. And we expect that this question may also be interpreted in a way that would give us an answer potentially to terminal sterilization. So we believe, actually, that the percentage using terminal sterilization -- not using terminal sterilization is even higher.

Third question, did you switch infant formula in the last two weeks, in order to gauge the brand loyalty question. One in four mothers have switched infant formula brands in the last two weeks at age one month for the child, and that drops down more or less continuously to one in ten mothers at nine months of age.

And finally, possibly most significantly, what type of formula did you use? Between 85 and 90 percent of mothers used powdered formula, as opposed to canned liquid infant formula.

To address some of the questions that you

had about Bisphenol A migrating from polycarbonate bottles, we've done an expanded analysis considering the experimental conditions and data available in the literature. We've divided those experiments into those that model what we call recommended use, and recommended use is extracted from World Health Organization guidelines, CFSAN infant formula guidelines, and guidelines from the American Academy of Pediatrics. And they encompass water boiled and cooled before mixing formula, no microwave heated, and that the formula is either refrigerated or used shortly after preparation. Those studies generally support a migration level of less than one microgram per kilogram into infant formula from polycarbonate.

An additional set of experimental conditions modify what we are calling current practices, which includes use in microwave ovens for heating and dishwasher use. Reheating studies we believe support a level still less than one microgram per kilogram food, even using microwave reheating, and less than 2.4 micrograms per kilogram food with excessive dishwasher washing.

The bottom line here, at least at this point in the assessment -- and again, I have to emphasize that this is an update and we're not finished -- that the expanded analysis continue to support the same or lower levels than our original assumptions. The exposure that we -- that we used in the draft assessment to estimate margins of exposures was actually based in part on the 10 microgram per kilogram food terminal sterilization assumption.

Moving on to ongoing activities -- obviously with regard to infant formula, we have a bit more to do laboratory wise. We need to complete our analysis of liquid infant formulas and of powdered infant formula samples that are included in our sampling process. We need to incorporate that new data into our updated exposure assessment model. And we also need to incorporate the information that we can extract from the ISPF II and the expanded PC bottle analysis, and any other relative data to the consumption into that probabilistic model. Finally, we need to incorporate an evaluation of the existing

biomonitoring data into the overall exposure discussion.

Other activities -- we have been engaging with the regulated industry to take part in what they may do voluntarily. One of those aspects is something we're calling a code of practice, which is essentially the development of detailed good manufacturing practices for the production of infant formula cans and for filling procedures for those cans to minimize BPA migration from existing packaging materials into infant formula.

We're also having ongoing discussions with polycarbonate manufacturers regarding the future marketing of polycarbonate infant bottles, which I believe Dr. Hentges alluded to just now. And of course, we're continuing our consultations with infant formula manufacturers as they are required to notify FDA regarding the use of -- regarding changes in infant formula packaging.

Toxicology ongoing activities -- we are doing what's left on that list of bullets that I began the talk with. We're reevaluating the studies

deemed adequate by the CERHR panel and expect to provide you with clear evaluation criteria for either leaving that -- bringing that data into the assessment or leaving it out. We're also evaluating the new data that the Science Board identified in its report and the new data that has been published since then. And we are considering the value of meta-analysis in bringing more value to some of the more disparate data that bears on this question.

As you're aware, based on the letter to Dr. McNeil, we are engaging the development of additional toxicity data. We have finalized a protocol to address some of the pharmacokinetic uncertainties, which will -- which is underway and will be performed in both rats and non-human primates, and we'll consider animals at a variety of developmental phases.

We're also developing -- we've approved in concept, excuse me, and are developing a protocol for a sub-chronic study that is part of a tiered approach to address the potential carcinogenistic and chronic toxicity of Bisphenol A. This study

will have expanded doses, expanded termination times, and a wide variety of expanded end points in relation to a standard sub-chronic study. It will be done in the NCTR Spragg-Dolly rat, and we expect this study to be the basis for designing the in utero two-year chronic carcinogenestic study, should that study prove necessary.

We're also engaged in protocol development for a neuro-developmental study in rats and for a study on growth, cognitive, and pubortal development in Reese's monkeys.

As Dr. Torti alluded to this morning, we're very grateful for to NIH for collaborating with FDA to begin identifying available cohort studies for assessment of temporal association of urinary concentrations of Bisphenol A with the incidence of specific diseases. That has taken the form of three FDA/NIH working groups. One working on the laboratory analysis of Bisphenol A, one working on epidemiology studies of infants for a variety -- excuse me, of adults for a variety diseases, and one working on epidemiology studies of