children for other endpoints.

Thank you.

Dr. McNeil: Thank you, Dr. Cheeseman.

I think perhaps we should pause to see if there are any questions from -- for this part of the presentation.

Garrett, you were on BPA Subcommittee, do you want to -- do you have any? I don't mean to cold call on you, but you're the most knowledgeable one on the board I think.

Dr. Fitzgerald: I don't know about that. Thank you very much for that exhaustive description.

I just actually had one question.

Dr. Cheeseman: Could you speak up?. I'm a little hard of hearing.

Dr. Fitzgerald: Sorry. I'm a well known mumbler, so we're a bad combination.

So, I was just struck by the fact that with your LCMS methodology, the concentration of BPA in food seemed to vary over three orders of magnitude. And while -- where the range sat was obviously quite reassuring, it's obviously a very

large range, and I just wondered if you had any insight into the sources of that variability?

Dr. Cheeseman: Yeah, the lowest values are limited protection values and I believe they're all powder infant formula samples. The actual variation is -- is somewhat smaller than for liquid infant formula. I believe it's .5 to 10.5.

And I don't -- I'm hopeful that we may get some information from the Code of Practice study that may be able to directly answer that question. Because undoubtedly it has to do with processing and -- either of the can coating or of the formula itself.

Dr. Fitzgerald: I suppose the other question that your presentation brings to mind is the -- well, the collaboration with the NIH is very felicitous and the opportunity to study samples collected in their large epidemiological studies would be particularly opportune. The same sorts of questions are relevant to that as are relevant to the JAMA paper that raised the question about the association with diabetes and heart disease, and

that is the stability of the methodology relative to the age of the samples. Many times in these large epidemiological studies, samples have been sitting around for a long time. And I just wondered if you were approaching that particular issue strategically and scientifically.

Dr. Cheeseman: I think we're discussing it, but I'm going to throw that question open to the other expert FDA and CFSAN scientists in the room who may want to step up to a microphone.

Dr. Torti: Since I'm not an expert in either of those, but I do a little bit of the details of the discussion. I mean, there is a very specific -- and Debra who is here can speak more to this -- there is a careful assessment of the stability of BPA in urine that precedes the analysis of these samples and the testing. So, to the extent that it is possible to look over time at the same sample and look at the decay of BPA over time in samples, this is being done and is planned and is part of the overall analysis.

Dr. McNeil: Other questions? I notice

you have the web address here, is that easy to find on the website or -- it looks kind of complicated.

Dr. Cheeseman: Our website's has been redesigned, so it's been my recent experience that not too much is easy to find. I actually haven't tried this.

Dr. McNeil: I wondered maybe if we could have -- Carlos, would you be willing to email us, the Science Board members, that complicated web address?

Dr. Russell: Garrett's undoubtedly the most qualified, I'm undoubtedly the least qualified person on the board to answer that question.

Dr. McNeil: I don't know about that.

Dr. Russell: I guess, because this is the first time I've really heard of this issue in depth, I'm trying to understand what everybody agrees rather than what everyone disagrees on. And I want to replay back to you what I think I heard and then ask you a question about Canada.

So, what I think I heard is that everyone agrees that BPA is toxic at some level. I think I

heard you say that everyone agrees that BPA leaches at some level. Infants can be expected to be more sensitive, but we don't know what level is toxic, really, and we don't know -- in humans -- and we don't know how much actually comes out.

So first of all, the first part of my question is, did I hear you right? Is that actually what we all agree on? If it is, what is it scientifically that Health Canada found -- if I understood correctly they've come up with a different approach and maybe you could just address that. If they did, what is it scientifically they found compelling in the context of what we agree on?

Dr. Cheeseman: Well, I think Health Canada -- I think it's important to understand that Health Canada acted under a chemical management statute and not under their food safety statute, and they acted in relation to polycarbonate bottles, which curiously enough is not under the jurisdiction of their packaging bureau.

That said, I believe, if you read the Health Canada assessment carefully, you will find

that there's not a great deal of disagreement, but they're acting out of an abundance of caution in relation to removing polycarbonate bottles from the market. So I think they have -- the difference is they're acting under a different legal standard.

Dr. Broach: I just want to get clarification of your answer to Garrett's question about the broad distribution. I was also struck by the fact that you go from almost no detectable levels to 10 micrograms per kilogram of food. And as I understand your answer, is that you can divide those into two cohorts, one is the powdered formula, which has very low levels, and the other is the liquid concentrate, which has much higher levels, and in that level the variation is lower, but even there it's 20-fold differences in levels. And the level that you're getting from the concentrate itself is much higher than whatever you get from the leaching from the polycarbonate bottles. So the concern, if there's any concern, would be in the preexisting levels in the formula. Is that a correct interpretation?

Dr. Cheeseman: Well, I don't think it's fair to take those numbers out of context because they need to be combined in the -- in a particular way. And, I don't want to dodge the question too much, but there, you know, based on those numbers, the likely contribution to the exposure would seem to be larger from the infant formula can, for infant liquid formula.

Now, that said, we're looking -- I'm projecting up here a range of values. I can't tell you whether that 10.55 value is a substantially lying out from the rest of -- the rest of the distribution. So I think, you know, extrapolating too much from some initial data would be dangerous.

Dr. Broach: The second aspect of the presentation, in the distribution curve that you showed of the likely BPA per kilogram of body weight per day that you put all the multiple factors together and came up with a distribution and you gave us the mean and the normal. It seems like the issue is the maximum levels and those should be where you're targeting your -- any future studies,

because it's not whether or not -- so if it's safe at the maximum levels, then it's safe for anything below. But if you find something that's safe at some 90 percent level, then there's still a 10 percent of the population that's receiving doses above that level. Is that also an appropriate way of thinking about this?

Dr. Cheeseman: Well, I don’t think, again, I don't think we're -- this is an analysis using the available data on BPA concentrations. It hasn't incorporated the rest of the information on uncertainties, with regard to the other factors. So, I don't think I want to necessarily comment on where we would come out on a 90 percent or a 95 percent or a 99 percent level. There are arguments to be made in relation to using any of those levels.

Dr. Broach: One final question. In the epidemiological studies, I can understand why you'd like to have data on what the BPA levels were in the infants and then do some sort of regression --

Dr. Cheeseman: I can't hear what you're saying.

Dr. Broach: I understand in the epidemiological studies you'd love to be able to have the BPA levels in the urine so you could actually do some sort of regression analysis of any effects and then tie those to levels of BPA. But there should be data on just bifurcating the population into those that were breast fed versus -- children that breast fed versus those that received formula, and to assess their other factors that would play in. But it should give you some hint about whether or not there was something -- some risk associated beyond some of the things we can assess from formula-fed babies versus breast-fed babies?

Dr. Cheeseman: Well, I appreciate that and I think, you know, we're still very early on in planning what we're going to do with the epidemiological data, and so we'll need to take that sort of information into account.

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

I think what I'd like to do is move on to

Dr. Sackner-Bernstein and here his part of this BPA presentation, ask questions of him and then if we need to, go back to some questions for the earlier part of the presentation. Otherwise I'm afraid we're going to lose people.

Dr. Sackner-Bernstein: Well, thank you very much for the opportunity to present to this panel and share with you our thoughts on how we are going to proceed as an agency to understand the public health impact of BPA on medical products or from medical products onto the patients who are in need of their use.

Before I delve in, I would like to make a couple comments as a presenter on behalf of the agency. It wasn't long ago that I was on advisory panels, having recently joined the agency, and I think it's worth pointing out that the impact that you can provide is much greater than you realize.

Often the FDA is not able to discuss all the follow up discussions that are held based on the input, but the input is quite valuable and ends up having much more impact than probably most panel

members understand.

The second point I'd like to make is that there were several comments in the public session about public confidence in the FDA. And again, as a new member of the agency I only wish you could see into what I've been able to see, in terms of the application of scientific principles and rigor of people within the team that I work, the center, and the Agency at large, on leadership levels and in terms of the staff that does most of the day to day work.

So, with that editorial statement behind me, the purpose of today's presentation is three-fold. First, I'd like to introduce the Science Board to the agency's approach for understanding the public health impact of BPA in medical products.

Secondly, we plan to make this presentation our commitment to present to the Science Board and circulate to you, as well as provide public disclosure, an investigational plan that outlines the specific steps we are taking in this initial phase of understanding BPA's role in

medical product safety. And that will happen within the next couple of weeks.

Third, we plan on utilizing today's meeting, as well as your review of that investigational plan, to get feedback for us to learn from additional perspectives with extra expertise and backgrounds that you all represent. Other areas that perhaps we should consider, ways we might approach certain of the questions differently or perhaps -- and of course part of us would like to hear this -- an endorsement that we're taking the right approach.

This importance of BPA in human health is well-described, based on the potential for interacting with estrogen-dependant pathways. And this has been discussed in many venues. Certainly this could be of greatest concern in the pediatric setting, as well as the in-utero settings specifically, as has also been discussed previously and alluded to earlier today.

The reports that BPA exposure has been statistically associated with adverse clinical

effects warrants attention, though it's important to note that these studies do not appear to show a link to the medical products, per se. And its importance, BPA's that is, is underscored by its presence in medical products, particularly devices.

The Science Board's Subcommittee heard last fall about the initial approach by CFSAN and you were updated in some recent documents as well as during the presentation today. And it's important to address the fact that the approach taken by CFSAN will be inherently different from that taken when we look at medical products, largely because the type of use of the product being regulated is different, and importantly, that the regulations that govern how we assess these products that are regulated, are regulated. So specifically, as presented last fall, CFSAN focused on the oral exposure route, as foods would seem to dictate. And their regulatory focus was on a safety assessment of the final food product.

In terms of the assessment of medical products, it's a bit different. The Center for

Devices and Radiologic Health, the Center for Biologics Evaluation and for Drug Evaluation -- well, we're going to focus on parental exposure studies, and I'll explain to you in the coming slides why that is the case. And very importantly, the regulatory charge is that we look at medical products, including BPA as a component of medical products, in terms of the risk-benefit ratio.

In order to assess the clinical risk -- and as we will outline in greater detail in the investigational plan -- we have two components. One is a safety assessment, which is focused largely on a literature review. The second is data-gathering efforts, and I will discuss this a little bit further.

The first component has already been completed wherein we requested information via a Federal Register notice. This docket closed in December and we're continuing to put together the information we received. That will be available to Science Board members as well.

We will also work towards quantifying BPA

exposure in patients from medical products and we will initiate our evaluation of alternatives to BPA, not because we believe at this point or we have evidence of this point that there should be other products, but rather to understand the alternatives.

The investigative plan is based on a three-step approach. I'll describe briefly each step. As you can see here, steps one and two are both required and feed into step three. So, I'll start out with step one, which is our exposure assessment. In order to perform an exposure assessment, we started with making the decision of how to prioritize the options. Several arenas have been the subject of attention from one source or another, and I've listed a few here in no particular order, that have garnished the larger share of attention.

We considered whether we should start with evaluation of dental products, certainly an area that has received a large percentage, a large portion of attention, in order to determine at what point dental products should be a focus of our

concern. The initial assessment is that exposure is very low, relative to that from food, with transmucosal absorption at the time of implantation of BPA-containing dental products, brief and at low levels. Therefore, we drew the conclusion that dental products would probably be an area that would be featuring a relatively low exposure.

Another proposal was to identify exposure from all medical products, but clearly that's not practical with the thousands of medical products that FDA regulates. Thus, the initial focus is on products that are likely to be associated with higher exposures, as well as those used in susceptible populations.

We determined that devices that allow parental exposure to BPA should be the highest priority for investigation in this initial stage. Direct blood contact to BPA-containing medical surfaces would seem likely to produce the more extreme exposure. There would be potential for significant leaching with the blood-device interface and there's no first pass hepatic metabolism to

conjugate the substance before having systemic contact. Additionally, exposure from medical devices is amenable to study based on standard pharmacologic principles, as well as international standards that I will refer to later.

Even those medical devices likely to be associated with higher exposures to BPA have clinical benefits allowing us to balance the benefits against the exposure, where those exposures theoretically could represent the potential for risk.

You heard from Dr. Cheeseman about the use of uncertainty factors in the calculation of tolerable intake values and understanding the importance and the relevance of exposure assessments. These are terms that come from the international standards documents that I referred to a moment ago and which I'll review in a little bit more detail in subsequent slides.

When I -- right here about reducing uncertainty, I'm not speaking in terms of that toxicologic view, I'm speaking in terms of just

having better information with more precise estimates.

So, focusing on that practical matter means that what we want to do is understand the potential impact of as a substance such as BPA, and in order to do so it's critical to make measurements to understand the range of exposures that patients may face.

It was alluded to by several speakers in the public session and in the FDA panel roster, that most of the work has been done in animals. And it's true that there are studies in people as well, but that's where we are trying focus, on the clinically relevant exposures in the clinically utilized situations.

And so we chose to do so in two specific areas in our initial investigation, and recently established collaborations with Children's National Medical Center and NCTR to perform an assessment of exposure for children undergoing cardiopulmonary bypass, and I'll refer in a few slides to what I mean by that.

Another collaboration was established recently with the University of Michigan. This gets at another setting where BPA-containing devices are used where there's a high likelihood of exposure to BPA, that is hemodialysis, and this study is actually being done on an established model for hemodialysis.

So why did we focus on these two settings in our primary assessment? Cardiopulmonary bypass is likely to permit a high systemic exposure to BPA via continuous and direct blood contact, wherein the entire body's blood volume is circulated through the machine while the heart does not provide any of the pumping capacity for periods of two hours or longer. This kind of open heart surgery, when used for children undergoing corrective surgery for congenital heart disease, is corrective. And the benefit can be easily seen in that instead of dying as disabled children, these patients can reach adulthood without limitations. So in the public health view, there's clearly net benefit.

CDRH is nonetheless investigating exposure

in children, because it's our belief as a center and an agency that merely the presence of a net benefit isn't enough, what we need to do is figure out if there are ways to make that net benefit as great as possible, maximize the benefits and minimize any potential risks.

The second model -- the second situation that we were focusing on is the model of hemodialysis. Hemodialysis or renal replacement therapy is likely to permit a high systemic exposure to BPA by a continuous and direct blood contact for four hours at a time, three times a week, chronically. These are for people with end-stage, non-functioning renal disease. This renal replacement therapy is life-sustaining, and instead of dying from kidney failure, patients survive with the possibility of reaching transplant. Once again, there's clearly net benefit. Our goal in studying this is because it's likely to be a high exposure setting, one where we can still try to make the benefit even greater relative to any potential risks.

The second step of our approach will be the toxicology assessment or the toxicity assessment. I previously referred it -- referred to an international standards document, specifically it's ISO-10993-17, which is a document that specifically establishes an international standard for how to evaluate the potential problems and how to interpret them within the construct of potential clinical benefit of a medical product that has leachable materials.

As an agency we propose to adhere to this international consensus on how to conduct risk assessments for compounds released from medical devices. The approach is conceptually similar to that used by CFSAN to derive ADI values and CDER to estimate first-time drug dosages in humans. This international standards document recommends accounting both for the risk of substances such as BPA, which is today's subject, and the clinical benefit of using these devices or products that contain that product, which in this case, again, is BPA. So it's advising risk, benefit, in comparison

to each other, consistent with the FDA's regulatory mandate.

What I'd like to do now is just present to you this list of the way we're going to be assessing toxicity from a literature review. And what we've summarized here is the characteristics of the study -- of the studies that we will include and the studies that we will consider including in our assessment.

The critical part here is that we are capturing studies with a broad net in order to make sure that as much information is included and any insights that we can gain are going to be useful. And this assessment is ongoing, there have been a number of people reviewing these studies already. We're talking studies well over 100 that have been reviewed already and I think the list is just likely to keep growing as this becomes a dynamic and living literature review.

One factor that may seem confusing is at the lower right, where it's clear from this slide, or at least it should be, that when we write studies

to be considered, they're not necessarily going to be in the primary data set. And we list ones where the effects of BPA are only seen at high doses, greater than 10 milligrams per kilogram per day.

The CDRH Toxicity Working Group has reviewed over 100 toxicology studies in animals. Many use doses greater than 10 milligrams per kilogram per day and some already have established that the no-adverse-effects level is going to be under 10 milligrams per kilogram per day. So in other words, where we're going to be safe is at a level lower than this value. If we already know that levels above this value or already believe that levels above this value are unlikely to provide additional clarity, in terms of where the no-adverse-effects level is, it doesn't make sense to focus on those and slow down the process, as part of our initial assessment. Nonetheless we are cataloguing these studies and they will be available for review if the information we gather indicates we need to look at them as well.

Step three of our process is the risk

characterization. I referred to the ISO documents before as an international standard document and these are some of the key points that the ISO document has. It tells us that we should compare exposure or the dose of BPA received by patients to a tolerable intake value. We are going to be measuring exposure in humans in controlled settings for the first time in the collaborations that I described previously, and it will be in children undergoing bypass, as I mentioned.

The international standards include transparency with regard to uncertainties and risk assessment and our intention in today's meeting, as well as providing our investigational plan, is to provide the transparency that people are asking for. It's critical for those scientists who are not part of the FDA to explain to the non-scientists that unfortunately science doesn't always work at the pace we want. It works at a pace that the studies can evolve. And therefore, while it might not seem we're being transparent, this -- today's meeting and that disclosure of our investigational plan should

be evidence that we are committed to transparency.

Third, and very importantly, when we're getting into issues of medical products, the ISO document establishes a concept that the acceptability of any leachable chemical, in this case BPA, that its exposure is to be determined on a case-by-case basis, depending upon the clinical benefit of the device or drug, whichever product is being evaluated, the availability and clinical performance of alternatives to the products that contain BPA, and the clinical status of the individual patient, as to whether or not the risk-benefit ratio is appropriate for that patient.

In order for the Agency to be prepared for the evolution of the science, of how materials and medical products interact, we needed to start planting our seeds and establishing our studies to see what alternatives there may be to BPA. Once again, I bring up the fact, and I'd like to emphasize, that the current data do not say there should be something besides BPA, rather because that is a possibility that products will be submitted for

review with other compounds, we are focusing on preparing for the advent of such submissions.

There is available information that suggests that there are several potential candidate replacements for BPA. Unfortunately, there's very limited information on the risks of these compounds. Thus, these alternatives pose unknown risks and unclear effects on device functions. CDRH is initiating preliminary assessments of several such candidates that could replace BPA, but because they are initial, by the very nature of such studies, these will include brief exposure in the preclinical setting.

As we move forward with finalizing our investigational plan and then carrying it out, we remained focused on our public health goal of striving to minimize risks while maximizing benefits. To do so, we continue our research, both internally and externally, and importantly, we look forward to providing you with our investigational plan and receiving your feedback today and in response to that document.

Thank you very much.

Dr. McNeil: Thank you very much as well, that was a lovely presentation.

I guess Garrett, I would ask you again even though this is slightly off the mark.

Dr. Fitzgerald: So, I commend you, actually, on the very structured approach that you're taking to the issue. And the only thing that sort of caught my attention as it went by, which I suspect reflects the nomenclature rather than reality, is that you consigned pharmacokinetics studies into the considered bin. And given that so much of the uncertainty here revolves around the accurate measure of exposure and its relationship to dynamic response, that would seem not appropriate, but perhaps that was just a nomenclature issue.

Dr. Sackner-Bernstein: Yeah, the reason for that -- and I'm glad you brought up that point -- is that what we're doing in that literature review is trying to understand toxicity. So when there's a PK study, a pharmacokinetics study that purely measure pharmacokinetics with no information

reported on any clinical effects, any effects on liver enzymes, any other physiologic parameters, but is a pure PK study only measuring drug levels, that's not going to be a primary part of how we try to determine what level correlates with potential adverse effects.

Dr. Fitzgerald: Well, I guess the bit of information you do have in those pharmacokinetic studies is how much of the material is delivered and you relate that to the measured concentration. And given that in the oral situation, in terms of what is delivered, there's so much variance as we heard about previously. And there's so little information as to how much variance there might be delivered into the systemic circulation. For example, in the setting of bypass, I think as much information as you can accumulate that relates -- that relates plasma concentrations to known amount delivered can be actually helpful to you in interpreting what might turn out to be a highly variable situation.

Dr. Sackner-Bernstein: Yeah, I suppose that the way could apply that, practically speaking,

is to say we have our literature review that focuses on toxicology, but we still need to know exposure. So those kinds of studies could be part of that review of what kind of exposure we get from doses, even if they only have PK studies.

The truth is, is you and I -- we all know -- most studies that are geared towards pharmacokinetics do include other parameters. So, they're likely going to fall into the bin of the studies we'd include, therefore from both perspectives. But I think your perspective of saying we should include that for exposure assessments is very valuable.

Dr. McNeil: Steve, you had a comment?

Dr. Spielberg: Thank you for that presentation, both for the science that's going to be done, as well as perspective.

A couple quick thoughts and then a broader comment. When you're doing the study on extracorporeal circuits, make sure you capture all other drug exposures. The reason I say this is that a lot of the drugs that are used, for example

propofol is in a cream form vehicle, and the vehicle may in fact change the rate of leaching of a variety different products, from IV tubing, from plastics, et cetera, et cetera. So just be sure that you're capturing everything that's being used and not just the name of the drug, but the actual product that's being used, whether diazepam or diazamul, which again can have differential effects on picking up products from a delivery system.

And the other general thing is, because PK is so influenced by extracorporeal circuits, I'd probably empanel some folks who have done pharmacokinetic studies on drugs in these settings, both dialysis as well as -- as well as cardiopulmonary bypass, so that you'll be able to get a better idea of when to really sample, how to interpret those samples with respect to steady state levels and before and after. Because lots of things go on in terms of volumes of distribution and everything else during the process of doing extracorporeal circuits. And there's a good deal of literature on the drug side that I think can

probably help inform that aspect of things. So, those are just two comments on those studies.

The broader comment and, you know, again I'm speaking as a pediatric clinical pharmacologist and knowing very, very little about BPA. I'm the new guy on the block and didn't even know about these discussions until a few days ago, which naïveté is helpful in this regard, so I can make some comments. And again, it comes to trying to draw heavily on the pediatric clinical pharmacology world. Those of us who study molecules that we call medicines versus those of us who study molecules that we call environmental chemicals or potential toxicants, because basically the same principles exist.

And I've heard so much discussion by enormously thoughtful and caring people throughout the room today about how to interpret data and the uncertainty that you talked about, Dr. Torti, with respect to extrapolation. And we have a great deal of difficulty extrapolating data from our rodent colleagues to us. We are continuously impressed

that doing developmental pharmacology often gives us grossly wrong signals about risk or benefit or pharmacokinetics of drugs when we then turn to looking at humans.

And I suppose the issue of extrapolating the animal data to the human data will be helped if, again, we do some of the things that we've done in pharmacology over the last numbers of years.

Okay, so we've got a molecule, this glucaronic data. That's not enough of a statement, we need to know which human glucaronic transferase is responsible for this. So, if it was the drug, we'd be screening against all the families of the glucaronic transferases to know which enzyme is involved, because each of those is on different ontogenetic regulation and develops under different timeframes. So to say glucaronidation is limited in the newborn isn't helpful at all, it depends on which glucaronic transferase is involved. And if we know that for something like BPA, that's going to help us model up and back between our rodent models and our human models.

Similarly, once you glucaronidate a molecule, it can be deglucaronidated by blucaronidates, and we need to know about that process between rodents and humans, and that may be important. In some of the differences between enteropatic recirculation and reavailability of parent molecule, which will give you radically different results in one species and another, incomparable levels of exposure.

So the issue of cross-species extrapolation will be helped greatly if we know something more about the human-specific pathways of metabolism of the compounds and their ontogeny. And we have increasing amounts of data on that, which we've had to glean from drug exposure and knowing about specific drug exposure and how that changes over time.

On the development or ontogeny of receptors or targets, is here too that we run into huge difficulties with respect to extrapolation, not only across species, but for that matter, from adult humans to kids because of a receptor that's present

in adults and we think the disease is the same in kids and we go ahead and use the drug, that receptor may in fact not be present in a six-month old, so the drug simply doesn't work.

So we're struggling similarly to the way the toxicologists are struggling to understand the ontogeny of those receptors. If you think about a mouse, okay, weaned at three weeks and reproductively capable at six weeks. Okay, as opposed to weaning, say at a year in a child, and a decade later going through puberty. The significance and the relevance of estrogenic or androgenic or any other steroid pathways or targets is going to be radically different with respect to timelines in the different species.

And so it's not just size and it's not just metabolism, but it's an entirely different construct in ontogeny and development. Guinea pigs walk at day one, mice don't for a couple of weeks. Okay, humans don't for a year. So, very different pathways of neural development as well, and the things that we're concerned about in higher

function, which, you know, going to school, succeeding in life, all the things that we want for our children, are so dependant on processes that aren't necessarily all that easy to study in animals. And Bill Slikker and others at NCTR have done heroic jobs trying to develop predictive models from neurotoxicity to what goes on in humans, but the gaps are still there.

So I suppose the thing that we're going to need to struggle with and we're going to have uncertainty no matter how good we get in the science and we're going to have to accept that. We will never know everything, that's not the way nature is. But to the extent that we can share knowledge that we've developed on the clinical pharmacology side in pediatrics with the toxicology side, I think we'll be better off.

So, in collaboration with NIH, I would put very strongly to involve the pediatric pharmacology research units, both in the PK studies that you're planning for extracorporeal circuits, but also for thinking about how to systematically look at the

development of these pathways in humans so that we have at least a better way of decreasing uncertainty when we extrapolate from either rodents or non-human primates.

Dr. McNeil: Thank you. That was a very thoughtful set of comments and ideas.

Dr. Sackner-Bernstein: I would just say that I hope you have time to look at the plan. That would be great.

Dr. Spielberg: Happy to help and I'm not the world's greatest pharmacokineticist, but I know who is. So, I can get them involved as well, because I think, you know, we're all struggling, we're all trying to do the right thing. No one here is trying to do the wrong thing and I think that's what message that needs to get out to everybody. And we're all struggling to understand nature and we're struggling to understand it in real time, which is the hardest thing because the science keeps changing.

But the good news is that I think there's a lot of richness in other areas of science, that if

we can sit down together we've got a chance of maybe doing a little quantum increase in our abilities.

Dr. McNeil: Thank you.

Are there other -- other questions or comments before we thank Dr. Sackner-Bernstein, as well as Dr. Cheeseman for their very thoughtful presentations and updates? And I suspect we're going to be hearing more from each of you almost every meeting. Is that right? Great. Thank you very, very much.

Are there any other general questions for members of the panel? I have a few things I want to say at the end, but I want to make sure that there's nothing that's left unsaid by us.

Alright, so let me just say a couple of things. I think we left one thing that may be left -- one thing may be left dangling. I'm not quite sure whether the board approved Dr. Torti's request that we establish a subcommittee to look at IT within the Science Board. And I would therefore like to get your permission to, if you agree, set up such a subcommittee. Are there any objections to

that? Do we need to take a formal vote, Carlos? Is it unanimous? Is anybody objecting to that wonderful idea?

[No response.]

Dr. McNeil: No, okay. People who leave early really get stuck.

And Lonnie King, at the break, had a really good idea and I thought I would say a word about it and then maybe we can see how it works at our next meeting. I think we were all very, very much impressed with Frank's discussion this morning about the FDA fellows and their credentials and their topics. They just looked spectacular and we've really only half of them. Lonnie suggested that while they do have mentors within the FDA, and we actually saw them according to each of their -- each of their projects, that it might be nice to have members of the Science Board, if interested, interact with them in ways that were appropriate, if their indeed are any.

So, Frank and Norris and Carlos and others, the staff here, and sector directors are

going to think about that between now and our next meeting, and see if there's a way, that where it's appropriate, members of this Board may be able to provide additional insight or just networking and mentoring abilities for these fellows.

If that turns out to be a good idea, we'll figure a way to get everybody together and it may be the night before the next meeting, something like that, but more to follow on that.

So, thank you, Lonnie, that was really a brilliant idea. So we will carry through on that.

And I learned today, actually, from Norris, I hadn't realized that our friend Carlos, Senior Policy Analyst for this Committee, has moved on -- or is going to move on to work -- still in the Commissioner's Office on nanotechnology. That's going to be an enormous loss I think for us. He's just been enormously helpful in not only just the logistics, but having a real understanding of a lot of the issues that we have to deal with, and in helping us think through the best way of getting the information before the board, before the public,

getting feedback, just organizing and thinking what's the best thing to do at what particular time.

So, we will miss you, Carlos. So I would like to personally thank you and I would like the board to thank him as well.

[Applause.]

Dr. McNeil: And then finally, one little technical note, I think it's finally, would the replacement for Dr. Zuckerman please come up and make sure we have spelled your name correctly. We don't want to do anything incorrect for the public record.

So, are there any other issues that we need to discuss? If not, I think we are adjourned. Thanks.

(Adjourned at 2:50 p.m.)