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Committee Conference Room
5630 Fishers Lane
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P A R T I C I P A N T S

John Doull, M.D., Ph.D., Chair

Gloria L. Anderson, Ph.D., Consumer Representative

Kendall B. Wallace, Ph.D., DABT, Chair,
Cardiotoxicity Expert Working Group

William D. Kerns, D.V.M., M.S., Chair, Vascular
Injury Expert Working Group

Industry Participants

Jack H. Dean, Ph.D., DABT
Jack H. Reynolds, D.V.M.
James Green, Ph.D., Chairman, Pharmaceutical Drug
Safety Steering Committee

Government Participants

David M. Essayan, M.D.
James T. MacGregor, Ph.D.
James Selkirk, Ph.D.
Daniel Casciano, Ph.D.
Helen N. Winkle

Kathleen Reedy, RDH, MS, Acting Executive Secretary

Frank Sistare, Ph.D., FDA Staff

C O N T E N T S

P R O C E E D I N G S

DR. DOULL: Good afternoon. I'd like to welcome you all to our subcommittee, Nonclinical Studies Subcommittee. It's a subcommittee of the Advisory Committee to Pharmaceutical Sciences.

We need to do a couple things to begin here. We need to be sure everybody knows everybody, so why don't we go around and introduce everybody. I'm John Doull. I'm a clinical toxicologist, and I chair the committee. Gloria?

DR. ANDERSON: Gloria Anderson, Callaway Professor of Chemistry, Morris Brown College, Atlanta.

DR. WALLACE: Ken Wallace, University of Minnesota, and I chair the Expert Working Group on Cardiotoxicity.

DR. KERNS: Bill Kerns, Pharma Consulting Inc. in Boston. I co-chair the Expert Working Group on Drug-Induced Vascular Injury.

DR. MacGREGOR: I'm Jim MacGregor from the National Center for Toxicological Research at FDA. I'm director of the Washington office here, and I'm the principal FDA coordinator for the subcommittee.

DR. DEAN: I'm Jack Dean. I'm the head of Preclinical Development for Sanofi-Synthelabo, and

I'm a member of the subcommittee.

DR. REYNOLDS: I'm Jack Reynolds from Pfizer, and I represent Pharma here.

DR. GREEN: I'm Jim Green. I'm from Biogen. I'm a toxicologist, and I'm currently Chairman of the Pharmaceutical Drug Safety Steering Committee.

DR. SELKIRK: I'm Jim Selkirk. I'm the Deputy Director of the National Center for Toxicogenomics at the National Institute of Environmental Health Sciences.

DR. ESSAYAN: Dave Essayan, Center for Biologics.

DR. CASCIANO: Dan Casciano, Director of the National Center for Toxicological Research.

MS. REEDY: Kathleen Reedy, Food and Drug Administration, Advisory Committees.

DR. DOULL: We have a couple members that won't be here. Jay Goodman won't be here, and I don't think Joy will be here. She'll be here tomorrow. And will Ray be here tomorrow, do you know?

VOICE: No, he won't.

DR. DOULL: Okay. I guess we'll go ahead, then, with the formal meeting statement.

MS. REEDY: Acknowledgment related to general matters waivers for the Nonclinical Studies Subcommittee of the Advisory Committee for Pharmaceutical Science, September 9, 2002. The following announcement addresses the issue of conflict of interest with respect to this meeting and is made a part of the record to preclude even the appearance of such at this meeting.

The Food and Drug Administration has approved general matters waivers for the attending special government employees which permits them to participate in today's discussions. A copy of these waiver statements may be obtained by submitting a written request to the agency's Freedom of Information Office, Room 12A-30 of the Parklawn Building.

The topic of today's meeting is an issue of broad applicability. Unlike issues before a committee in which a particular product is discussed, issues of broad applicability involve many industrial sponsors and academic institutions.

The committee members and invited guests have been screened for their financial interests as they may apply to the general topic at hand. Because the general topic impacts so many

institutions, it is not prudent to recite all potential conflicts of interest as they apply to each participant. FDA acknowledges that there may be potential conflicts of interest, but because of the general nature of the discussion before the committee, these potential conflicts are mitigated.

In addition, we would like to disclose that Drs. Jack Dean and James Green are the non-voting guest industry representatives. They are not government employees and, hence, we do not screen them for conflicts of interest and can make no comments on their actual or perceived conflicts of interest.

In the event that the discussions involve any other products or firms not already on the agenda for which FDA participants have a financial interest, the participants' involvement and their exclusion will be noted for the record.

With respect to all other participants, we ask in the interest of fairness that they address any current or previous financial involvement with any firm whose product they may wish to comment upon.

A couple of housekeeping things before we begin. On the right side of your blue folder is

the agenda and the background material for the two topics to be discussed today. On the left side are the materials for tomorrow's discussion, and these are all the absolute latest versions of these documents. These documents are also on the Advisory Committee website, the address of which is at the bottom of your agenda.

Ron would also like a count of how many people would like to go to dinner at Copeland's tonight.

[Pause.]

DR. DOULL: Are there any comments about the statement of conflict of interest? You all feel you're off the hook?

[No response.]

DR. DOULL: The purpose of the meeting today, we have three things in mind. It's been a while since this subcommittee has been updated on what's been happening with our working groups, and both the Cardiac Working Group and the Vascular Working Group have really made an awful lot of progress. So we felt it was really important that the subcommittee hear about the activities that are taking place with those two subcommittees.

The third item of business has to do with

a home for this committee. As some of you know, we've been debating back and forth exactly how to do it, and Food and Drug has made some recommendations. And so we need to talk about that today, and we'll do that after the break. Helen will come down, and we'll spend some time discussing the future of the Nonclinical Subcommittee.

Dr. MacGregor, do you have additional--

DR. MacGREGOR: I guess just my only comment is that having attended some of the working group meetings, both these groups have been working really hard, and I'm looking forward personally and I know those of us at FDA are looking forward to the discussion today because both of these groups have come to a point where they have formed some of their own preliminary conclusions, and they'll be presenting those today, and we'll be all looking forward to feedback from the committee.

Also, I'd like to thank Jim Green for taking the trouble to come down. I think one of the hopes we had when we put this committee together was that we could build a structure to interface with our major stakeholders and to identify those areas of common interest that we

might pursue collaboratively. So as Chair of the PhRMA Drug Safety Committee, we're very happy to have him participating in the meeting today, and also, thanks to Jim Selkirk for substituting for Ray Tennant, who we were happy to have on this committee as a representative both of NIEHS and the National Center for Toxicogenomics. And since Ray wasn't able to make the meeting, we're very pleased to have a representative from the National Center for Toxicogenomics participating in the meeting.

DR. DOULL: All right. I think then we'll go ahead and proceed with the cardiac component. You have slides, Ken?

DR. WALLACE: Yes, I do.

DR. DOULL: Okay, great.

Oh, yes, I guess before we--we missed you going around.

DR. SISTARE: Frank Sistare, FDA, Center for Drug Evaluation and Research.

DR. DOULL: I think we got everybody else.

DR. WALLACE: Well, thank you for this opportunity to report back to the NCSS on the progress that the Expert Working Group for Drug-Induced Cardiac Toxicity has made since the last time that we addressed this group.

It's my personal privilege to represent this working group because it's staffed with very capable and engaging members on the Expert Working Group, and we've had very productive discussions. The most recent was about two weeks ago as we tried to bring this to some sort of forum for the NCSS.

If you recall, the last time that I addressed this committee I updated you on our progress at that time, and we had had a workshop where we discussed troponins as possible biomarkers of drug-induced cardiac toxicity, and I also presented to this committee our intentions of developing a report, a written report on the status of troponins as biomarkers.

One of the feedback items that I received from this committee was that the committee wanted to have an opportunity to inspect the outline of this document before it took on too much of a solid form so that the committee could have an opportunity to contribute to the development of the document and have some input. And so that's one of the first things that I would like to do today.

There are basically three orders of business. I'm going to come back to this with the last slide, but there are three points of

presentation today.

The first point--and that will take most of the time--is to go through the outline of what we hope will be the final report concerning troponins. That's the first item agenda, and that outline is in your blue folder, and it takes the form of this kind of form. Hopefully you've had a chance to review it.

The second thing is that during the course of developing this outline, the Expert Working Group identified some data gaps, information needs, and I'd like to have an opportunity to discuss with the NCSS some plans that the Expert Working Group would like to pursue as far as filling those data gaps and information needs.

And the third and final thing that I would like to present to the committee is the Expert Working Group's opinion that we need to look beyond the troponins and look for additional biomarkers, the next generation of biomarkers, of different forms of drug-induced cardiac toxicity, and I'd like to present that to the subcommittee and to get some favorable feed-forward on that.

So if we can go to the outline first, we'll walk through that.

Again, this is an outline of a document that will hopefully eventually be published in the peer-reviewed literature. But the purpose of that document basically will be to assess the current status of the scientific information, the evidence that supports or doesn't support troponins, I or T, as valid biomarkers of drug-induced cardiac injury to be used both in nonclinical and clinical drug evaluation studies. Along that process we hope to identify situations where in the troponins could benefit the nonclinical studies and to identify barriers and knowledge gaps that would limit such benefit. So that's the overall purpose of this proposed document.

I suggest that the document will begin with a justification why we even have to look at biomarkers of drug-induced cardiac injury, and we hope to support the need for this, justify it based on two primary points. One is the attrition of drugs during various clinical phases of development and the cost that becomes involved when you lose a drug during clinical trials, as well as postmarketing attrition of drugs once they have already gained the registration.

We then will move on. We're already using

clinical biomarkers, so the second part of this document will be saying, well, what are the limitations of the currently used biomarkers in drug-induced cardiac toxicity, and we'll speak in terms of three different issues. One is specificity, sensitivity, and inter-species differences.

The specificity currently, the current biomarkers of drug-induced cardiac toxicity fall short of the mark as far as specificity. Most of these proteins that are found in serum are also expressed in noncardiac tissue, so they're not specific to cardiac tissue. And oftentimes there are documented cases where you will get histopathology, cardiac histopathology with no change in these biomarkers. So there are several examples of false negatives, if you will, with the CK and myoglobin and other examples of the current biomarkers.

There is also the issue of sensitivity. The current biomarkers that we have in hand, are they sufficiently sensitive that we can catch an adverse cardiac effect early in its development prior to having irreversible damage? And at this point, they seem to fall short on that.

Then the third point is the interspecies differences. For the most part the current biomarkers--again, this is creatinine kinase, myoglobin and such. There's a lot of interspecies variability, and, therefore, it makes it very difficult to bridge between two animal species, let alone between nonclinical and clinical studies. And so that represents a major limitation to the current biomarkers. So there is indeed a need, a significant need for better biomarkers of drug-induced cardiac toxicity.

Then after we have developed the document with the justification and rationale, we'll move into the introduction of the biomarkers and what constitutes a biomarker. And we presented this in a different format at my previous address to this committee. The Expert Working Group has identified four different types, categories of biomarkers of cardiac toxicity: There's markers of structural damage. There's types of functional damage--one is mechanical, contractile damage, and the other one would be electrical or dysrhythmias caused by drugs; the long QT syndrome is a good example of that. And then a fourth type of category of toxicity that we've identified is one of

homeostasis, where as a result of a stressor, the response is the tissue will undergo alterations in gene expression or, as an example, to establish a new steady state, a new homeostasis where it can survive secondary insults. This would be like the remodeling or the conditioning that happens with several tissues.

So there's four categories, and when we start talking about any given biomarker, we'd be remiss if we didn't remember that we have to identify which category of toxicity or damage this element, this molecule is marking.

We've also talked about the characteristics. Once we identify a biomarker, what are the characteristics of an ideal biomarker, and we presented this the last time that I addressed this committee, and that is that the biomarker has to be specific, in this case specific to the heart tissue, ideally not expressed in other tissues. It has to be sensitive. It has to be sensitive. It has to be released early in the pathway of pathogenesis, hopefully well in advance of reaching the point of no return, of irreversibility. It has to have favorable kinetics so that the diagnostic window is sufficiently

broadly that you can catch it, you can observe it, detect it after the drug insult.

The assay itself has to be robust. It has to be simple, it has to be inexpensive, accurate, reproducible. And then the fifth characteristic of an ideal biomarker would be that there would be very little differences between species. That assay would be useful in bridging between both nonclinical and clinical studies. You could transfer that platform, that technology easily between those scenarios.

So we introduced the biomarkers in that section. Now we introduce the troponins. In this section we'll talk a little bit about the biology, how the troponins are a part of one element of the contractile complex, the thin myofilaments, and it participates in the contractile process and just some basic background biology of the troponins, the different forms of the troponins, T, I, and C.

We'll also talk about the multiple isoforms of troponins, the T, I, and C, and how these may vary between tissues and such, along that line.

We'll then get into characterizing the troponins as a biomarker of drug-induced cardiac

injury. And, again, we're going to look at these five points: the specificity, sensitivity, kinetics, assay, and whether it's a bridge between nonclinical and clinical. And I'll talk extensively about this in the next couple pages. And as we go through these five bullets, they will then reveal where we have limitations and data gaps within these five characteristics.

So based on the discussion the Expert Working Group had on August 28th and 29th, we arrived at some fundamental conclusions, and two of the conclusions regarding the specificity of the troponins T and I are that they are perhaps the most highly specific of the currently employed biomarkers of drug-induced myocardial injury. These components--these are--two isoforms of the troponins are expressed exclusively in the cardiac tissue. They're not expressed in other tissues, even under pathological situations.

The Expert Working Group also concluded that the appearance of either of those troponins in the serum would signify a generalized disrupting of the limiting cell membrane or the disruption of myofilaments and the leakage of the troponins from the cell. That's what it signifies. That's the

type of damage. It's a structural damage, and that cardiac injury that does not result in altered cell permeability would not necessarily be reflected in a change in the serum troponins. So there can be--there are several examples of where troponins may not change in response to cardiac injury.

As far as the sensitivity, in reviewing the literature, much of which is at least referenced in an abbreviated form in the written document before you, the Expert Working Group concluded that the serum troponins I and T, as long as they're measured in the critical diagnostic window, they're highly sensitive indicators of myocardial injury. They're as sensitive as the other biomarkers that are currently in use.

Also it was concluded that the serum troponins are detected as early, if not earlier than most of the other biomarkers in response to drug-induced myocardial injury, so they are sensitive.

With the kinetics, the troponins are released during the active phase of cell injury, and once that cell injury stops, the serum troponin level would return towards control or a baseline, or perhaps a new baseline, and so there is a

critical diagnostic window. An exception to this would be a case such as with the anthracyclins where you have a progressive myocardial cell injury where the troponins would rise in the serum and they would remain elevated for a long period of time. As long as there was active cardiac cell injury occurring, the troponins would stay high until that would finally terminate and then come back down towards a baseline.

In review of the literature that we had available, a very thorough literature search and review of that literature, it was deemed that the increase in the serum components occur in proportion to the extent of cardiac damage.

We looked in brief at the assays that are used to measure the serum troponins, and it was the opinion of the Expert Working Group that they are simple, accurate, reproducible, and fairly inexpensive. So they are robust.

Perhaps what's key with the characteristics of the troponins is that they are very good--have very high potential for bridging between nonclinical and clinical studies. The amino acid sequence is conserved across the species. The antibodies to human troponins

cross-react with the cardiac troponins from a variety of different animal species. The cardiac troponins are expressed to less than 1 percent in non-cardiac tissue of humans, and the same is true for those non-human animal species as well. And, therefore, it looks like these are very good candidates for bridging between nonclinical and clinical studies.

Some of the limitations that the Expert Working Group came up with in the reviewing of the literature is that we have issues of the critical diagnostic window, and, of course, the working group considers that that diagnostic window will be defined on a case-by-case basis depending upon what the specific drug is and its dosing regimen of that drug. So that will be a moving diagnostic window that has to be better defined.

Another limitation is that the assay for the troponin T is available from only one vendor at the moment. The troponin I assay is available from probably 6 to 12 vendors currently.

Another limitation is that the baseline values, at least quantitatively, change in serum. They may be altered by disease. Whether it's a muscular degenerative disease, a tumor, or

whatever, that baseline may--does seem to float, at least on an experimental basis, and so that a validation assay would definitely have to take into account the fact that that baseline would be changing. So we'd look at a -fold increase and not just the absolute value.

And the final point is the validation of the individual assays. With so many assays out there, there's a lot of differences between assays, and it's very important that the monoclonal antibody that is used is directed at the specific epitope that remains conserved between the different species for that particular cardiac isoform of that troponin. So assay validation.

We then looked--so that's the outline as it is, is that basically the committee reports from the literature that troponins seem to--are perhaps the most appropriate biomarker of drug-induced cardiac toxicity that is available, and they're specific. They're as sensitive as the other biomarkers. They mark a specific type of damage, not all types but a specific type of structural damage to the cell. The kinetics are such that once we have defined the critical diagnostic window, it would be useful in those terms. The

assays are robust, sufficiently robust, and they are conserved across species so they're excellent bridging biomarkers.

However, there are some weaknesses or data gaps that need to be addressed to gain additional confidence in troponins as biomarkers of cardiac toxicity, and that is that based on available evidence, most of which is clinical evidence, but based on available evidence--well, first of all, most of the data that's in the literature for troponins I and T derives from clinical studies, usually myocardial infarction types of studies. And so there's a need to gain a better weight of evidence from nonclinical studies, from animal studies, to make sure, build our confidence that the animal studies will mirror the human studies as far as the specificity and sensitivity of the troponins.

So we need to gather more nonclinical, more experimental animal data to further validate the troponins.

We also have the question of that the Expert Working Group is quite uncertain whether--which is the preferred marker, the troponin T or the I isoform. At this point the

data even in the clinical studies is insufficient to suggest that one is superior to the other. And so the question is: Do you measure one, do you measure the other, or do you measure both? And at this point the data--there's not enough data there to really draw any conclusions.

Another weak point where additional data would be helpful is better characterizing this critical diagnostic window, the rate at which the troponins increase and then the duration of that increase before it returns to normal, and correlating that with the histopathology and the pathogenic process, mechanism, mode of toxicity would be very helpful.

And then, of course, to further validate that the troponins are marking one specific type of cardiac injury, and that is the cell lysis, the alteration of cell membrane permeability, and that cardiac toxins that do not affect cell membrane permeability are not necessarily reflected or associated with changes in troponin. So just to make sure that we can know what type of toxicity they're discriminating through.

The Expert Working Group talked about how we'd go about gathering this non-human--this

nonclinical data, and what we propose to do is at our next meeting of the Expert Working Group to have a very comprehensive discussion of what kind of data is most needed and how we perhaps would design experiments to gather that type of data, and then based on that, then it would kind of dictate just how we would go forward with it, whether it would be done in-house or through a consortium or perhaps trying to get some RFAs issued to gather that data. But at this point we don't have enough of a discussion on this that we can propose any of those at the moment.

The other data gap that we feel, the Expert Working Group felt was needed is better substantiation of the nonclinical, the clinical correlations, comparing the kind of data that we'd get in the animal studies with that which has been generated in the clinics. And here we're actually--to approach this, we probably have to do some data mining. You're looking at data that already exists either within the agency or within PhRMA, and developing sort of partnerships where, through various organizations, ILSI being one of them, where the stakeholders that are involved in this process can come together and share that data,

yet retain their confidentiality to any proprietary advantage that they might have with it. So the Expert Working Group would like to look into the possibility of bringing these different stakeholders together in such a forum to share data and address the issue of the correlates between nonclinical and clinical validity of the troponins.

The third item, third bullet in that first slide or the second slide was approaching the next generation of cardiac biomarkers. Again, I remind you that troponins look to be the best biomarker, according to the Expert Working Group, the best biomarker available for drug-induced cardiac cell leakage, cell disruption. But that's all they mark. They report it. They don't predict it. And so what would be ideal is if we had a biomarker that would change in anticipation of an irreversible event with a cell. And so we feel there's a real need to look at biomarkers of other types of cell injury that perhaps don't involve changes in cell membrane permeability, and especially those biomarkers that may occur early on in the process that would give us a predictive advantage. And we propose, again, the Expert Working Group, to get together first as a group to

discuss this area, and then to plan a meeting, a much broader meeting of the stakeholders to bring the stakeholders together again in some sort of forum where we can have an open discussion of what some of the most promising biomarkers may be, whether they're existing kind of biomarkers or perhaps taking advantage of some of the emerging technologies with the old mix and such. So the Expert Working Group hopes to move in that direction as well.

So I remind you of that second slide, and I would really like the NCSS to address these three points. I'd like to have a lot of feedback and exchange of the outline of the document that the working group hopes to draft within the next couple of months. I would like the permission, authorization, approval of the NCSS to move ahead with the plans that the Expert Working Group has for addressing the data gaps concerning the troponins, as well as the same types of plans to move ahead for looking at additional biomarkers of other types of drug-induced cardiac injury.

So that concludes my presentation. I'd be more than happy to answer questions. I'm real pleased to see that there's a couple members of the

working group that are in attendance, and I'm certain that they would be very happy to help as well.

DR. DOULL: Thanks, Ken.

Questions from the--Jim?

DR. MacGREGOR: Before questions, I thought perhaps I might acknowledge the other working group members that are here and who are available to participate: Elizabeth Hausner is here in the audience, and she's the CDER liaison who participates in the working group. Gene Herman is a scientific member of the Expert Working Group. David Essayan is the CBER liaison to the committee, the NCTR liaison. And then the working members of the group--I may mention I notice they're not in the packet, and we apologize. We should have had them listed. So at some danger of omitting someone--check me--I'll mention who the other members are that are on this group, and I should also that two of these members have just themselves prepared very comprehensive reviews of the troponin literature that will be appearing soon, and that's been a valuable resource to this committee. Those two members are Gene Herman, who I already introduced, and Malcolm York from GlaxoSmithKline,

who both will have comprehensive reviews appearing soon.

Other members are Gordon Holt of Oxford GlycoSciences; Alan Metz of Pfizer; Elizabeth Murphy of the NIEHS; Rosie Rosenbloom of Schering-Plough. And I think that's it. I don't think I've forgotten anyone. Okay. Sorry for that diversion, but I thought it would be--that we should acknowledge who the members were.

DR. DOULL: Absolutely.

Questions for Dr. Wallace? Yes, Bill?

DR. KERNS: Ken, that was a very good presentation, a good summary. Thank you.

You mentioned a couple of times the window of opportunity for timing to catch troponins when they're elevated. Can you talk a little bit more about that? On the practical side, is it realistic? That's my question.

DR. WALLACE: Thanks for that, Bill. It's going to be on a case-by-case basis. Basically there's two compartments for the troponins. Back to basic biology. There's a small fraction, 5 percent or so, that is free troponin in the cell, and then the majority of it is bound to the actin filaments. It is believed that immediately after

an abrupt injury to the cell, you have an immediate release of that free fraction. So you have an abrupt increase in serum troponins. That then is followed by a more prolonged release of what used to be the complex, the bound fraction, into the serum.

The kinetics of that, I would say that you start first seeing the troponins appear--it depends, like with an MI, as an example, within the first hour, and there will continue--they might continue to increase from between 4--peaking between 4 to 12 hours. Gene, is that kind of--yes. So there's plenty of time to catch the window. Again, the objective is to see an increase, not necessarily grab it at its peak.

What's nice is that the control, the baseline serum value of troponins is near the detection limit of most of the assays. So basically any increase above that is a remarkable increase.

Yes?

DR. ESSAYAN: Yes, Ken, it was a great presentation. One point of clarification which I'm sure is in your plans, but didn't come through as explicitly as might be necessary. In correlating

the preclinical to the clinical, I assume you're going to be looking also at the pharmacokinetics and handling of the troponins across species to assure that appropriate and analogous measurements can be made if you're going to look at comparisons of preclinical to clinical data. And I don't know offhand the elimination half-life, say, of troponin in mice compared to humans compared to dogs, things like that. I assume it's roughly the same. But there will be data in this paper that will look at that as well, or is that adequately described to put into the paper?

DR. WALLACE: As far as the paper document itself, I'm not sure how much detail will be given to this correlation between the nonclinical and clinical, and it's just a matter of timing. The intention of the Expert Working Group is that this document would be prepared within the next few months; whereas, to get the stakeholders around the table and mine the data would take much longer than that. So the document itself may conclude that there are these limitations or these concerns where additional evidence is needed.

As far as the actual development of that discussion, you're absolutely right. We have to at

least--we have to consider the kinetics of the troponins. We're also going to have to face whether we're going to mine the data or we're going to generate new animal data that would hopefully mirror, parallel what already exists in the clinic. And that's a discussion that hopefully this group will have at that time. Thank you.

DR. DOULL: I'd like to go back to the three things that you've asked the subcommittee to address. One is improving on your draft. Certainly, I think the subcommittee recognizes that this is an excellent draft, that this would be a very scholarly paper on troponins and used for cardiac toxicity. The intent then, your plan, as I understand it, is that you would put together this draft of the paper which would deal strictly with the troponins. All those alternative biomarkers would be down the road for another consideration. And the intent of this paper, then, would be to make the argument that these are effective clinical biomarkers and nonclinical bio--bridging biomarkers, really, and, therefore, should be considered for use, for that use.

DR. WALLACE: Let me answer that by saying I purposely kept that slide to three bullets, so

the data gaps is a separate bullet from the document, as is the next-generation biomarkers. So the document is stand-alone without those two. So the document will be focused, just as under the outline of statement of purpose. The purpose of the document will be to assess the evidence on the troponins. To assess the evidence on the troponins.

DR. DOULL: Okay.

DR. WALLACE: And that's it. It will be focused just on that.

DR. DOULL: My impression, looking at your conclusions and summation and so on, is that you're making a fairly strong recommendation that your committee feels, in fact, these are pretty good biomarkers, and that there's a pretty good argument for making some kind of a recommendation.

DR. WALLACE: Well, I remind you, my committee was not asked to make a recommendation. My committee was asked--our committee was asked to weigh the evidence and evaluate the evidence. And you're right in your perception. The committee, when they look at this, the committee feels that the troponins are--of our choices that are currently available to us, troponins are perhaps

the biomarker of choice, are the words that the working group used. The troponins are the biomarker of choice for drug-induced cardiac cell injury.

DR. DOULL: The reason I'm asking that is that, you know, if you make that kind of recommendation, that recommendation would come from your Expert Working Group in some--

DR. WALLACE: To the NCSS. We report to this subcommittee. So we will make a report that will assess the current state of the scientific evidence on the troponins. We'll write that up, and we'll give it to this subcommittee.

DR. DOULL: Okay.

DR. WALLACE: As far as the published document, that's a separate manuscript, and that will still--since it's going to have the aegis of coming through this subcommittee, we'll definitely want the subcommittee to review it before we submit it for publication. But...

DR. DOULL: Yes, I guess, you know, in a previous discussion, I guess at the last meeting, we talked about the fact that Food and Drug, in fact, is involved in it because it is a subcommittee of the Advisory to Pharmaceutical

Committee and so on.

This paper could be published simply as a paper by your work group and would then stand there as a recommendation in the peer-reviewed literature. What you're saying is that you want it come through the process so that this subcommittee is going to be involved in a sense with you in this paper.

DR. WALLACE: Yes, that's a good point. What will happen is the working group has decided that we want to publish this paper, and that the authorship will be the same no matter how we do it.

What we'll want to do--and I'm going to speak for the committee, for the Expert Working Group, without actually addressing this at one of our discussions. But my impression is that we'd bring it to the Nonclinical Safety Subcommittee and we'll say: Do you want to sign on? Do you want to be, you know, a footnote, an acknowledgment that it came through the subcommittee? Or if you want to have no part of it, then that's fine, too. But we'll give the NCSS first opportunity to have it come through the subcommittee. And if they say no, then hopefully they'll still give the blessing that the individual members of the working group can

still publish it independently.

DR. DOULL: Yes, I think there are two aspects to that. One is that, as I understand it, there are some regulations that get involved here, particularly if you publish it, for example, and, you know, we put on there "Subcommittee" and all that. That has some implications, and we need to be sure that we can--you know, the appropriate procedure for doing all that.

The second thing, I think, is that in the paper, as you've proposed it, you're talking about some limitations of this and some data gaps that would be--should be filled, and then that would be part of that paper, how you would approach filling--handling that data gap situation.

T1B DR. WALLACE: Not necessarily. Defining the data gaps would be part of the paper, but I don't know--after talking to the other authors of the paper, I would think perhaps just identifying the data gaps, and it may stop there.

DR. DOULL: Yes, right.

Dr. Selkirk?

DR. SELKIRK: Yes, this kind of harkens back to your presentation about the kinetics of things. You mentioned that troponins are elicited

immediately, and I wondered, especially in nonclinical studies, what that might mean, meaning is this measuring in peripheral blood? Because there has to be some kind of a time lag from the insult to when you would begin to see the troponins appearing. And I was wondering if any studies had been done, possibly with things like cardiac puncture, to see exactly when the troponins begin to be elaborated. And, furthermore, is there a gradient in the cardiac tissue where you begin to see troponin appearing in terms of cutting through the tissue itself? I'm thinking in terms of how genes are turned on to begin this process and what the pathway to it might be. Clearly it's early, and I apologize for not having a better knowledge of the troponin literature, but have those studies been done, fairly early timepoints to exactly see what the kinetics are?

DR. WALLACE: Yes, and if you'll allow me to draw from my recollection of the literature--and hopefully I'll quote the literature correctly.

Gene Herman has worked with doxorubicin extensively, and with the low doses of doxorubicin, I believe you first start detecting values of troponin in rats above baseline at both the 2- to

4-hour point.

[Inaudible comment off microphone.]

DR. WALLACE: No--well, I'm going to talk about that. Doxorubicin is about 2 to 4 hours?

[Inaudible comment.]

DR. WALLACE: Oh, those are lower doses. Okay. Lower doses of doxorubicin, it was taking like 12 hours. So with an acute dose, like with isopurinal (ph) or isoproterenol, the values appear in the plasma about 2 hours, I think--

VOICE: Within one hour.

DR. WALLACE: Within one hour.

DR. MacGREGOR: Excuse me. If members of the audience comment, could they please use the microphone so they can pick it up on the transcript.

DR. WALLACE: Sorry. Sorry for getting you in trouble here.

DR. MacGREGOR: Why don't you summarize Dr. Herman?

DR. WALLACE: What Dr. Herman clarified, with the model that he's done with doxorubicin, he's given very small doses on a weekly basis, one milligram per kilogram or so to a rat. And it isn't until 12 hours or so that he seems them

appearing. But those are very small doses.

If he does an acute insult to the heart with something like isoproterenol and another group has done isoprenaline, there you see the values of troponins rise above baseline within an hour of the dosing.

There's also been studies done with the isolated perfused Langendorf(ph) type of heart where they'll do just a physical impact of it, and they'll see it appear in a perfusate within minutes. So it is a fast release.

DR. DOULL: Jack?

DR. REYNOLDS: So, Ken, one thing that wasn't too clear to me is you talk about data mining with FDA on PhRMA. What would that look like? And what would you be wanting to get from such data mining?

DR. WALLACE: Well, the state of the evidence or the state of the science with the troponins right now is that it's being used quite extensively, but it's not being reported in the public literature a great deal. So the Expert Working Group is of the opinion that there's a lot of data that exists within PhRMA, as well as within the agency, that will be helpful in assessing the

utility, the validity of the troponins as biomarkers of drug-induced cardiac toxicity. And so the data mining would be to sit the respective parties around the table and come to some sort of agreement to a mechanism by which that data can be made available to the Expert Working Group for our assessment of sensitivity, specificity, kinetics and such to see--you know, check the validity of these as nonclinical markers. But it's with all respect for the proprietary nature of the data that we're asking for.

DR. DOULL: That's a complicated issue and one that, you know, involves a lot of things. If you're talking about proprietary information and how do you protect that and how will it be dealt with in a peer-reviewed paper out in the literature and so on and what is the role of this subcommittee and Food and Drug in accomplishing that, that validation you're talking about is a crucial point and a difficult one. I think it requires careful moving in order to get that done properly in such a way that will really help us get what we need to get done.

DR. WALLACE: That's, again, why the validation, the data gap, you know, that's a

separate bullet from the document itself.

DR. DOULL: The task of the subcommittee is to help you, but I'm not sure exactly how. That's complicated, Ken. We'd need to think about that.

Jack?

DR. DEAN: Ken, I'm a little confused, and maybe you can clarify for me. In the body of the outline and the review of the literature, you talk about the correlation between the clinical and preclinical. You give some examples where with various compounds there is some correlation between clinical and preclinical. At least that's the way I interpret it. But in the conclusion, you talk about the gap between clinical and preclinical.

So is the intent to talk about the utility as a bridging biomarker of the troponins? Or is to say that in the human it's well established, in the animal we don't have enough data to know? I mean, I guess the bottom line for me: Is it the intent of the working--is it the feeling of the working group that these really are at a point of being bridging biomarkers? And are the data there from the preclinical side to say that's the case?

DR. WALLACE: Well, I believe that the

Expert Working Group would conclude that the data that we have available at this point would suggest that there's very great potential that these are excellent bridging biomarkers, but there is certainly a need for additional data in the preclinical side.

Does that answer your question?

DR. DEAN: Not entirely. So you're going to review the preclinical data as part of this. That's what the outline seems to indicate. You're going to review what exists in the literature on the preclinical data.

DR. WALLACE: Yes, that's what we've done so far. We've only been able to access data that's available in the public domain. So we've looked at all the peer-reviewed and all the published literature on the troponins.

DR. DEAN: And then you'll define data gaps, and this will be--what?--the correlation between preclinical and clinical. And will the paper then set out a work plan for what should be done? Because it seems like that would be one of the greatest utilities of the paper, to describe these gaps and how they could be filled.

DR. WALLACE: Well, that goes back to an

earlier question, and in there I say basically we just identified a gap, and without giving a lot of work to how we would address them. But perhaps you're right. Perhaps a second sentence in that same paragraph saying that in order to address this we'd have to bring the parties together, you know, to create an environment where they can share the existing preclinical--either generate new preclinical data or mine that which is already there through, you know, an agreement between the various parties.

DR. DOULL: Those are both recommendations. One would be to get the existing clinical data that's hidden away someplace and use that. The second would be to actually undertake a research program, to go out and get animal data to find out something about the kinetics of those.

DR. WALLACE: Right, and I would guess that it would have to occur in that order, too, that you'd mine the data before you'd generate any new data. Because if the data's in existence and if you can evaluate it, why repeat the experiment?

DR. DOULL: That's really true, that there's a lot of data there.

DR. WALLACE: We have the impression that

there is.

DR. DOULL: Food and Drug has a lot of data that would be helpful in dealing with this issue, or PhRMA.

DR. WALLACE: We have the impression there is, and so what we're looking to is to work with the subcommittee to devise some sort of venue to bring these parties together to have an open--to discuss these data and yet protect the interests of the participants at that table.

DR. DOULL: Good.

DR. DEAN: Mr. Chairman, could someone just address the question you raise? Is there a lot of data there that needs to be mined, or is there sufficient data to do any mining? Because if the recommendation is we mine and there's nothing to mine, it would seem better to have a recommendation more around some sort of prospective study.

MS. HAUSNER: Ken, maybe you would like to break that down into the--

DR. MacGREGOR: Could you identify yourself?

MS. HAUSNER: I'm sorry. Elizabeth Hausner, the CDER liaison to the Expert Working

Group. There are several types of data that we are hoping to be able to mine. I think, one, we can divide into what PhRMA has and what FDA has. And as far as I'm aware in CDER, there is not a lot of preclinical and nonclinical troponin data. I think there is a hope that perhaps we can identify problems in cardiac toxicity that with use of troponins might have been picked up earlier, respecting, of course, the proprietary nature, and make this perhaps a numbers thing. And then, Ken, perhaps you would want to address in more detail what we're hoping to mine from other areas.

DR. WALLACE: I'm not sure where you're going with that, Elizabeth. It's my impression that PhRMA has generated a lot of troponin data. They have a lot of data. Now, apparently they're not submitting it to the agency.

MS. HAUSNER: Last year at the American College of Toxicology, when we had our symposium on clinical and preclinical use of troponins, there were quite a number of people from PhRMA in the audience who approached the microphone and shared their companies' experiences. But it's data that we have not seen published. So there does seem to be a fair bit of exploration of troponins

preclinically.

DR. WALLACE: Very little of which has been submitted to the agency, so most of the mining is going to be done on the PhRMA side, apparently.

DR. DOULL: You also mentioned that there are these different kits and that the results are somewhat--is that a problem also, that you have to figure out, you know, those variabilities within the different kits?

DR. WALLACE: Yes. Whenever you have an antibody-based kit, you're going--the specificity and sensitivity of the assay is going to depend upon that antibody. So you have to be very cautious in designing the antibody to target the epitope that is conserved with specific isoforms. We call them the first generation. We're not as specific as subsequent generations of the antibodies. And so now there are several kits out there, and there has to be some sort of validation or normalization of the kits, or the procedure by which you use any individual kit, so that what you're looking at is a full change or you have an internal standard that you can incorporate into whatever kit you use, you use that internal standard as a benchmark to assess whether you see a

change or not. But these are all, you know, things--issues of validation that a group has to sit down and deal with.

DR. GREEN: Just one point of clarification. You mentioned that the kinetics of the troponin with respect to onset of release of the soluble early form is quick, relatively rapid, and then it tails off. Is that correct?

DR. WALLACE: Well, I don't know if really tails off before the second phase starts in, kicks in, so it's more like a shoulder.

DR. GREEN: But early phase of leakiness, essentially, with cardiac target cells. To the extent of the data, certainly we can take the query back to the PhRMA Drug Safety Steering Committee and ask specifically, but I would hazard to guess that those companies that perhaps have experienced cardiotoxicity problems with their drugs may have embarked upon follow-up mechanism-of-action studies where they have that troponin data or other experimental markers early on. But these early-on sampling points usually aren't routine with the bulk of the studies which are done. So it's much like the analogy for toxico-kinetic exposure sampling that years ago, before people realized

that this was an important qualification, a way of presenting exposure and dose, these samples weren't taken at a point in time when there was--there might be essentially meaningful data measures.

So I wouldn't be surprised that we don't have an awful lot of data, even with broad-based member companies, but I think much of this is probably related just to the way that the bulk of the studies have been conducted in the past.

DR. WALLACE: That's a good point.

DR. DOULL: You might get some idea about troponin on troponin T also from those early clinical things, maybe.

Yes, Jack?

DR. REYNOLDS: So Jim kind of alluded to what I guess the nature of my question was in terms of the data mining. I don't think as a matter of routine that at least our company--we don't use troponin that much as a screening tool there. So I'm not sure how rich the database would be.

Also, the notion that we generate data around troponin and don't submit it, of course, if we had a drug in development, when we were going to seek approval of that, we would submit those data. So it's those drugs that may have troponin data

that never made it to clinical development or we stopped development on. Those are the data that would not be submitted. So, again, I'm not clear as to how rich the database would be around troponin.

I do think what could be done, though, is to look at those drugs that have had a cardiotoxicity potential liability based on nonclinical studies or even clinical studies, and from that in the database of those compounds that had that attribute, I think both partnering with FDA but also industry, one could go back and use those as models and generate data with troponin. That would probably be, I think, the best way to mine the database, not for troponin per se but for drugs that may have caused that.

So if I might ask another question, Mr. Chairman, around the discussion of who publishes a paper or under what pretext it's published, certainly it seems to me that this committee ought to endorse this publication, and I would think the Expert Working Group--I know you said that you would make that recommendation back through this committee. I understand that. But it seems to me that probably the most value from this publication

other than its scholarly review of the state of the art of troponins would be to provide some endorsement as to the merits and value and even limitations of troponins as markers of cardiotoxicity.

So, in my mind, if that were done as an independent body, not through this committee, that would have one weight of, I guess, credibility. But if it were to come through this committee where there is, in fact, this open partnership of regulatory agencies and they're regulated to have some endorsement of this as being an appropriate--at this time, anyway--measure of cardiotoxicity, I think would be certainly consistent with the objectives of this committee. And so if we were going to take that to a vote, that's what I would suggest, that we try to do that: one, to make a recommendation, if possible, if the Expert Working Group would say that, that this is a measure of cardiotoxicity; and then this committee try to endorse that recommendation.

DR. DOULL: Hopefully the subcommittee would do more than peer-review this paper, that they would be involved, because you are our working group and we're looking for ways to help you do

something that will benefit the clinical use of new drugs, bridging biomarkers. That's what we're really looking for. And if we think this is a good one, why, we really ought to somehow get on the bandwagon.

I guess, you know, if you look at this as a weight-of-evidence kind of argument, your weight of evidence is going to lead you the conclusion that you think is ready for prime time, pretty much. But then the question is: How much is that weight of evidence impaired by the data gap? And it isn't just the one data gap, Ken. You know, you listed several of them, and you've talked about getting clinical data, the clinical data that's out there, and if we're lacking animal data, that maybe we need to study to do that. But there are some other--you know, you have some other data gaps that you've talked about. And I guess in a sense in that paper, these have to be addressed, also, because if you're going to do a weight-of-evidence kind of evaluation as a basis for your conclusion, then one is going to have to look at some of those other data gaps, I guess.

DR. WALLACE: Again, I'm going to take a risk of giving you my personal impression about

this, Dr. Doull. I think it might reflect the consensus of the committee, the working group, but I'm not certain because we haven't discussed it as a group.

Where we draw the line and publish this paper kind of depends on whether it's going to be the seven of us as independent authors and we'll then title it "The Current State of Knowledge," and that would be fine. Identify where the holes are and what might to them, but not address them, and that would work, and then maybe a year from now or two years from now, do "The Current State II."

However, if it comes through the NCSS, the NCSS may decide that you're not comfortable with that and you don't want to publish it until the data gaps are more thoroughly addressed. And that's fine. You know, we're a working group of the NCSS. And if that's what you would like to do, excellent, you know, we'll be very happy to pursue that. But we need that direction from the NCSS, and then if the NCSS wants us to address these data gaps, we need help in convening, in formulating this venue, where we convene the parties under conditions that they can share this data that we wish to mine.

DR. DOULL: And I think that really gets to kind of the heart of it. This committee would like to have ways to figure out how to get--if, for example, you need a nonclinical evaluation of troponins in animals, for example, you need the study done, then this subcommittee would like to have some options to recommend. This is one way you might get this done or, you know, this is a source of funding that you might seek to get these studies done or something. And right at the moment, we have not really crystallized exactly where we--have we, Jim? Dr. MacGregor is going to tell us.

DR. MacGREGOR: Well, no, I just thought I might comment on my perception of what are the expectations of the working group and the subcommittee, and, Kathleen, correct me if I'm accurate on the rules. But my understanding is that the subcommittee we have formed as a fully public venue for addressing the mandates of looking for scientific opportunities to improve nonclinical practice and to then, through the parent Advisory Committee, make recommendations on implementations of studies to fill gaps or to perhaps pursue regulatory implementation.

The expert groups were asked, my belief is, to assess the state of knowledge, identify where we are, lay out paths forward to fill these gaps, and then present them through the subcommittee for recommendation.

So the expert groups, to my understanding, wouldn't be making--wouldn't be the ones to make the recommendation for either implementation of collaborations or regulatory follow-ups, but would provide the base of knowledge upon which to make those recommendations.

So the hope is that through the work that these committees have done, the subcommittee then can identify areas where you feel there should be collaborative follow-up or where you feel there should be a recommendation to change current practice in some way based on this knowledge of the biomarker. And part of the reason for this is because the subcommittee and the Advisory Committee are always fully public with advanced notice through the Federal Register, et cetera; whereas, the Expert Working Groups, although we have kept them public and we have issued notice for all the expert groups and kept them open, there is not the same degree of public involvement; that is, there

is not always a formal Federal Register notice before meetings and so on. And so for that reason, the knowledge should come forth and recommendations should then issue from this level.

DR. DOULL: Actually, we have two kinds of--we can make some recommendations to your committee, your working group, Ken, but we also would be thinking about recommendations that we would make to the Advisory for the Pharmaceutical Group Committee.

Frank?

DR. SISTARE: I think we're going to get a little more clarification later when Jim, Dan, and Helen speak. But in my mind, this group, as Jim has just pointed out--there are always going to be data gaps. You know, every good research leads to more questions. There are always going to be data gaps, and this group is going to define and maybe prioritize the data gaps. I'm not sure. But they're going to define the data gaps that exist.

Then there's sort of a bifurcation. Someone needs to make a decision. Are the data gaps so broad that more research is needed? If that's so, then I believe the vision for the NCSS, without stealing the thunder of what's going to

come later, would be that more research needs to be done, and there's a committee that's going to oversee that research.

If, on the other hand, the decision is made that those data gaps are not real big right now, someone decides this is ready, as you say, for prime time, for implementation into regulatory and drug development practice, then that would go to a different committee, and then that committee would need to, you know, in a very public way, make that decision, yes, we're ready here. It may be case-by-case. It may be investigational talks, maybe something like this, or it may be it's going to be measured every time. Every time you take a clin chem measure we're going to include troponins.

So that's going to come with time, but I think we have to sort of wait to see, you know, how this document comes out in terms of how big are those data gaps. I will say that this is a very unusual situation in the sense that all of these assays have been, quote, FDA approved for clinical utility for myocardial infarction. So this is a very immature biomarker, if you will.

We can haggle over, you know, which kit, what's the baseline that this one measures, and,

you know, what big of a change is significant or not. But there are also two very austere bodies which have decided that cardiac troponins are going to be truly, you know, thought of as a gold standard in this sense for myocardial infarction now. So any time there's any kind of ischemic injury, they're going to rely on cardiac troponins in clinical practice.

So this is a little unusual, and it's a very interesting scenario that we've set up. We may be at the point where we're ready to say let's get some more nonclinical experience with these things right away, let's start implementing the regulatory practice. We feel the assay is well validated, at least analytically validated. They're FDA approved. To say that they're not would be difficult, I think. But to say whether or not they're appropriate for this species or that species or this species is something that we need to probably enumerate.

So this is an interesting situation that we're in here, and this is probably the first time, you know, for any biomarker to come across this mature and to say are we ready to start changing practice here.

In terms of the data that's available, I would agree, there's just not a lot of data that we have within our own data files. There is some. There is some. I know that there is some troponin data that has been submitted. But we've heard Malcolm York talk to us about a lot of the data, those generated on compounds that haven't come to the agency. So, you're right, I mean, it's not data that's not coming to us in any sort of intentional way. It's just it's not an IND yet. So I'm not sure how we can get that information.

One big gap, though, I think, is if you can talk a little bit about some of the gap areas. You know, one that comes to my mind is the issue of specificity. And I'm talking about biological specificity. Are there drugs which are cardiac-active but yet not cardiotoxic that may cause a release in troponin? I don't know how many examples of those that we've evaluated and how clearly we can define that boundary, because that is going to clearly be, I think, a major concern to sponsors to be able to define, you know, that boundary line.

So I think we need--that may be a gap that may be important to define before it's incorporated

directly into regulatory practice. I don't know. There were certainly a lot of success stories, but I don't know how many people have invested in things. I know we've done a little bit, like, you know, Cisplatin, you know, and get kidney toxicity, but let's make sure there's not some reversion to some fetal isoform of a smooth muscle troponin that shows up and interferes with the assay and we haven't seen that. But those kinds of things, there are hints of those kinds of things in the literature and the clinic, so there may be some things like that that need to be done. I don't know.

But I don't know if you can address some of those things. You talk about some of the kinetics, and those would be good for our reviewers to point to a paper and say, you know, we would like to see you do an analysis of, you know, whether you pick up a biomarker to see the histopathology of what you're seeing in your study. Would you please look at troponin? Well, when do you want me to look for it? You know, it would be helpful to have a good document we could point to to sponsors and say, you know, we feel that this is a good time to start looking at these things.

DR. WALLACE: Thanks, Frank. You raised a couple questions that I'll try to address.

What is the specificity? And you talked about some isoforms reverting back to the fetal form and being picked up, they're not cardiac reactive.

Based on the animal data, the nonclinical data, there is evidence in the literature that you'll get--the cardiac isoforms will be released into the serum in response to some non-cardiac toxicity. The questions that we're not certain of as a working group is: Is that because of an artifact of the antibody that was used to detect the cardiac isoform? That would be one possibility. There was enough hesitation that I'm not sure that if you used the newest generation of antibodies you would pick that up of cardiac troponins increasing in response to a non-cardiac toxicity.

The other thing we talked about is we talked about cardiac drugs that are cardiotoxic but release troponins. We didn't talk about that so much. We talked about situations where you'll have like nephrotoxicity and you have a cardiotoxicity that is secondary to the kidney damage, a volume

effect, blood volume effect, and you get the release of troponins. Well, if you see the troponins increase there, is it a--it's not a primary cardiotoxicity, it's a secondary, and we have to kind of understand that a little bit better.

But when you look at the nonclinical data, what you're drawing from as far as drugs, most of your nonclinical data--of course, it's only a small fraction of what the clinical data is. But other nonclinical data is available. Most of it is perfusion-related data, ischemia, reperfusion types of stuff.

What's available in drugs are the anthracyclins, doxorubicin, daunorubicin, isoproterenol and isoprenaline. And I don't know if there's any other published literature of any other drugs out there. So as far as a primary data need it would be--whether data mining or data generation, is to look at other drugs, especially those to see if we get any false positives, because, of course, the false positives and false negatives don't appear in the literature. So I think there's value to look at the data that we do have, at least, to get a better handle there.

DR. DOULL: I think it's clear that the process that has been established is the correct process, and the process is that the working group does a weight-of-evidence evaluation and makes a recommendation that comes to this committee then; and if this committee feels that's a good recommendation, we support that recommendation in the proper thing and then carry that on up the ladder. That seems to me to be scientifically the appropriate way to go to get the job done.

I guess then in terms of the specific things you've asked us about the outline, I think by and large we are enthused about the outline.

Gloria, did you have any--you like the outline. So, you know, that's going to produce, we think, a very scholarly paper and one that we can clearly endorse.

The second thing you're really asking is support for the recommendations that you're going to make to fill the data gaps, and I guess in part that depends on, you know, whether you recommend data mining, which you're recommending, as filling part of it, but whether you then go ahead and recommend additional animal studies or additional other kind of studies. I guess we'd have to look

at those to see precisely whether we're on the same team as you guys in terms of those recommendations.

I think the third thing, the alternatives, I guess that's a down-the-road thing. It's going to be a long-term committee. Ken, don't plan on retiring because once you get through with the troponins, why, obviously, then you want to come back and take a second look at some other things.

It would be kind of nice in this paper to say--you know, you've already said there's nothing out there that's as good as, but there may be some hints out there that there are some coming down the road, there are some significant things that deserve study.

DR. WALLACE: Basically, those are the questions I'm asking of the NCSS that you addressed right there. One is--well, as I recall, the Expert Working Group was convened to look at biomarkers of drug-induced cardiac toxicity, so more than just the troponins.

DR. DOULL: Right.

DR. WALLACE: The indication to look at--get a suite of biomarkers that would mark most types of drug-induced cardiac toxicity and not just one type. And in the process, of course, we'll be

very anxious to look at the developing technologies and see if there's something on the horizon that we can perhaps kind of spearhead and get a springboard to its development. So that's Item No. 3.

Item No. 1 and 2 kind of go hand in hand. Of course, the Expert Working Group, this whole analogy--this is a whole new situation within the agency, as I understand it. The working group says, well, we're going to deliver this document to the NCSS. The next question is: Are we done, or do you want us to address issues of addressing the data gaps? Do we just identify them, or would you like us to continue to have input into the NCSS and try to, you know, help convene sessions for data mining or develop--help identify what types of data need to be generated?

So we're really bringing it back to the NCSS. What would you like the working group to do as far as the second and third points?

DR. DOULL: I think, you know, our goal is to get the whole job done, which means that we improve the clinical--or using biomarkers in the clinical introduction of new drugs, both nonclinical and clinical, that whole business. So it's the whole package, in a sense, that we're

looking at, and I think our hope is that through this working group process that we, in fact, develop a mechanism which facilitates that long-range goal.

DR. WALLACE: Well, I think the Expert Working Group would be very agreeable, very anxious to continue on both filling in the data gaps with troponins and looking at the next generation of biomarkers. But we're not certain that that's what we're being asked to do. We're not certain that we're being charged to do that.

DR. DOULL: And we may have to leave that, I guess, until we hear from the session following this in which we're going to talk about the mechanism of how this subcommittee really fits into the whole process, because that would help us answer that question of how best can we help you guys.

I had a couple of very minor little points. You talked about the classification of biomarkers, and I think we had talked one time before about biomarkers of effect and biomarkers of--monitoring biomarkers and so on. There was kind of a classic--

DR. WALLACE: Biomarkers of exposure

versus biomarkers of effect.

DR. DOULL: Okay. And you now have a different group of--a different classification system there somewhat.

DR. WALLACE: Well, these are all biomarkers of effect.

DR. DOULL: Okay. So--okay. So within that previous classification we talked about, there's still this classification.

The other thing that you mentioned, Ken, that struck me, you pointed out that new drugs, 80 percent of them are lost because of toxicity and so on. But that 80 percent, what percent of that is cardiac? Isn't it mainly liver that's--when we lose all the new drugs? It isn't cardiac effects that is the major cause, is it?

DR. WALLACE: Not to my understanding. Of course, I'm not in the field, but talking with friends who are, I understand that the incidence of adverse cardiac effects in the clinical phase is fairly small.

DR. DOULL: Which would be useful to kind of mention in--

DR. WALLACE: But I don't know what the incidence of failure in the nonclinical paradigm

is. And this is a nonclinical.

DR. DOULL: Well, that's true, and that's really part of what you need the biomarker for.

Yes, Jack?

DR. REYNOLDS: I think based on our portfolio, if you're talking about structural cardiotoxicity, that is to say, troponin release, histologic changes, it's not that common. But if you're talking about--and I'm reluctant to use the word, but other manifestations of cardiotoxicity like rhythm and rate changes, that's extremely high in terms of attrition. I don't know the exact number in our portfolio, but it's high, like--probably the foremost cause of compound in our portfolio dying are from QT prolongation and other dysrhythmias that we cannot predict. So that's very high.

DR. DOULL: See, I think that would help to put that in. It helps focus as to what the problem is and why we really need a good cardiac biomarker.

DR. WALLACE: Yes, and that's what we're trying to include in the justification and rationale section of this.

DR. DOULL: Do other members of

the--Gloria, do you have any other comments? I think what we're saying is that, you know, we like the outline, we want to help with the data gap solution once we figure out exactly how best we can help giving advice. But we are going to expect the weight-of-evidence decision to come from the working group, and then we would then respond to that.

DR. WALLACE: How about the third bullet as far as the additional biomarkers? Should the Expert Working Group continue on--

DR. DOULL: Yes, my feeling is you'll just dilute out your effort. You know, it's hard--you guys got a great paper in the making here, and if you wait around to get all the other options, you know, you could have a chapter on genomics and proteomics and PET scanning and the whole-

DR. WALLACE: Well, it would be a second document.

DR. DOULL: Yes, that's my feeling.

DR. WALLACE: If we launched any work into the next generation of biomarkers, it wouldn't be at the expense of this. It would be that we'd start growing it. We would launch that effort and start growing it as we're finishing up the troponin

work.

DR. DOULL: Okay, how about other committee members? Jack?

DR. SELKIRK: Could I make one point? I'm sorry. With that regard, as you launch to the next phase of this, and you mentioned for data gap filling emerging technologies, and you mentioned proteomics and genomics, and I think they will go a long way in terms of redefining or refining what you have in the pathways to other biomarkers, and there may be precursors to troponin in terms of its biosynthetic pathway that may even be earlier. That is why I asked my question earlier, even at an earlier time point, which may be diagnostic. So, these, I think, will be extremely helpful in the future.

DR. WALLACE: Maybe prognostic.

DR. DOULL: So maybe they should spend a little time looking--researching that area.

DR. SELKIRK: Yes, I would think so. I would think that probably there is not much out there in the public literature in terms of data mining, yet using array technology. But I think it's ripe to be used in this way, and I think it would produce tremendous amounts of information in

terms of gene pathways and viable proteins in the pathway, too.

DR. DOULL: It would be nice to cover that so that you don't get sideswiped by somebody coming along and say if you wait three months, we'll have a genomic array that would give you the answer to that.

DR. WALLACE: Well, again, I share your enthusiasm there just on a personal level. We started with the troponins, as you said, John, that it was mature. Or it was Jim who said that it was already mature, and it was the obvious first marker to look at.

But now as we are bringing that to conclusion, at least near conclusion, the committee is saying, well, what is next or is that going to kind of sunset the committee with the troponins, or should we continue to look on at alternate biomarkers or alternate types of damage, or should be worry about devising schemes for filling up these data needs in that, so we are just bringing those questions back to the NCSS.

DR. DOULL: It is my feeling that the consensus of the committee is that we certainly expect this working group to go ahead and follow

down this path. You know, you have made a great start, and now we should see that through.

Yes, Frank?

DR. SISTARE: To help address that question, because it is going to be complicated to answer that, to begin this process, we went through a number of steps to get to the point where we identified these two areas. We will hear about the other one tomorrow. But that is not to say that there aren't five or six or seven or eight or ten other ones that are important to address. So now it is going to come down to priorities. How do we establish our priorities? How do we choose where to put our efforts next? And then I think it is going to come out of the--you know, we are going to hear how this committee is going to move into a more research-oriented arena, and a parallel world will be set up in a more regulatory arena. That regulatory world is going to say these are our needs, and that research world will say we can get those, we can solve those for you, you know.

So, I mean, just without going through the formal process of committee, you know, like we have a research subcommittee that helps prioritize these kinds of things. But we are seeing compounds that

are causing, you know, as Jack pointed out, you know, the rhythm-type toxicities. That clearly is a major issue. You know, ILSI is doing some--you know, expending some efforts in there. If the perception is that that effort is going to solve the problem, we may not, you know, set up a committee here.

So there are a lot of other factors that go into the decision of what would be the next thing to do. But I would also say--and then our committee acknowledged that right up front when we were deciding options. We mentioned that the QT issue is a very important one to the agency that needs some attention. But we felt that some of those things are being addressed. I still think there are other needs in there that need to be addressed, and we are working through some mechanisms to get that done as well.

But there is another issue, and you brought up the mechanical. You know, the drug-induced, sort-of hypertrophy response, whether it is direct or indirect edema. We don't know sometimes. But the agency is seeing this happening in a non-insignificant frequency. And our clinicians do wrestle with: How can we monitor for

this in the clinic? Is there a biomarker that we could be using to help with that?

So, you know, if we were going to end this episode here as coming attractions, that might be something that, you know, we need to think about. So, again, we haven't gone through the formal process yet, but I would just leave and say that that is an important issue to our center, and we do need to solve it one way or another. Whether this is the mechanism that is chosen or not, other people will have to certainly enter into that decision. But I would vote in favor of that.

DR. WALLACE: Well, that's basically what my questions are: What is the life span of this committee? Is it going to limit itself to the troponins and sunset there, and start a new committee to look at the volume-related effects or the rhythm effects, and that be a whole new Expert Working Group? Or is it same committee and perhaps add additional new members and continue along that line?

The urgency here, and before I surrender the microphone, I am going to ask the Chair here that we have--we're tentatively scheduling the next meeting of the working group for November 8th or

10th--something in there, I forget--to coincide with the ILSI biomarker one. And whatever this NCSS decides as far as data gaps and next generation of biomarkers is going to drive the agenda for the November meeting on the Expert Working Group.

So before we leave tomorrow, I really do need some clarification.

DR. DOULL: And let's do it that way. After we hear the discussion, the rest of the discussion this afternoon, and after we hear the vascular presentation, then I think we'll be in a better position to come back and talk about this issue.

One thing. You know, the Vascular Biomarkers Group has some information, I think. There needs to be some talking to one another because you guys have talked about biomechanical things and so on, and in reading that, I had tended to feel, well, there's something in there maybe for both.

When this committee was established, you know, we were looking at all kinds of biomarkers, the PET scanning, and we looked at genomics and we looked at all the liver effects, for example, and

focused on troponin because it seemed like it was out ahead, and vascular, because that was a clear need that had to be addressed and nobody else seemed to be addressing it; whereas, genomics, there's a lot of activity going on in there, and we're hoping that that's going to feed somehow into our working groups, and also ILSI's doing that, you're doing that, Dan, your group, and NIEHS. So somehow, you know, we need to benefit from this collaborative--but that's really what we're talking about, is the goal of this committee is to find good biomarkers. The second goal is to find good biomarkers that are not only preclinical but are clinical, bridging biomarkers. The third goal is to get everybody involved, to get the public involved, to get the pharmaceutical industry, academia. And in doing those three things, I think hopefully we'll work this all out.

Do we have other--Gloria, do you have any-

DR. ANDERSON: I'm find.

DR. DOULL: Anybody else have comments?

MR. PAPOIAN: I just wanted to give--

DR. DOULL: Give your name, would you?

MR. PAPOIAN: Tom Papoian, Center for Drugs. I just wanted to give another way for the

subcommittee to think about how we can help the everyday reviewer who has to deal with making recommendations for additional animal studies when their case arises. A hypothetical scenario would be, say, a multi-dose study done in animals where, upon sacrifice, when you do a histological examination of the heart, you find damage, you find necrosis. And this is, say, at the height of some large multiple, what could be a therapeutic dose.

Most divisions, reviewing divisions, would have some problem with that because they don't know how that would relate to therapeutic dose, whether that would occur in some individuals and not others, how would they monitor for that.

What I would like to do is to recommend an additional follow-up study where you do another study and measure troponins.

Now, I feel sort of my hands are tied at this point to make that recommendation because of the gaps that we have in that knowledge, whether such a study is appropriate based on the current knowledge of whether troponins actually reflect drug-induced injury in animals.

If that information were available and there is consensus available that such

recommendations are a good thing to do, a study could be done and showing that, yes, troponin levels only increase upon a large multiple of a potential therapeutic dose. And, further, one can monitor for such toxicity in patients, and the clinical trials can proceed because you can also monitor troponins in ongoing clinical trials.

So from a recommendation of nonclinical studies, having some additional for how to best recommend additional animal studies in which troponins can be measured would be very useful.

DR. DOULL: I think the subcommittee has no problem supporting the science of that recommendation. It's the mechanics, I think, that we haven't exactly decided how best to support that.

Jack?

DR. REYNOLDS: Yes, I think Tom pointed out what I was going to say, too. I think an important part of this committee, as opposed to activities like the ILSI activities, is that through this committee and the expert working groups and the deliberations of this committee, it seems to me like we should be able to provide some endorsement of a biomarker or a model or an

endpoint that has some regulatory standing, if you will. I think for many of us, that's really kind of one of the difficulties we have.

For example, we may be working on a compound and we think a particular biomarker or model is our recommended endpoint, if you will, around a particular toxicity. Well, others may disagree with that or others may have data, especially FDA may have data that would contradict that. So we could end up, let's say, internally supporting some biomarker when, in fact, the reviewing agency or the individual reviewers know that that doesn't have the weight of regulatory practice, if you will. So I think that's an important part of this committee, is to help define the science, define the gaps, but to be able to bring that back to regulatory practice, both so that the regulated industry knows what they need to do to demonstrate a lack of or the presence of certain toxicity, but people in regulatory agencies can do that and do that in a public forum in which all stakeholders can come to the table and deliberate the merits of the endpoint we're talking about.

DR. DOULL: This committee should be able

to do that.

Any other comments that we want to give to the cardiac--Jim?

DR. MacGREGOR: It seems, listening to the discussion of the last few minutes, that there are an obvious couple steps that need to take place, and I would suggest that the first step would be--which I think has already been taken--if the subcommittee is in agreement that the outline is appropriate and this should proceed to a formalized report with references, I would think that would be the first step. And I might also add, with regard to that, I believe we did have a discussion about the scientific publication a couple meetings ago, and that there was encouragement that basic findings that this expert group had produced as this report could be published as a scientific review article and that there not only wouldn't be a problem, but there was encouragement, I believe, for that.

The second step would be the consideration by this subcommittee of the report and the gaps, and to take a position on the kind of questions that have just been raised in the discussion. In other words, after reviewing that report, does it

suggest that this is the preferred biomarker? And if it is, then perhaps there should be a recommendation that the agency needs to consider when that use is appropriate and that the agency should put out some guidance, perhaps, on that. If there are major gaps, then hopefully this subcommittee could recommend how to proceed to fill those gaps. And perhaps, I think, from what Ken was saying, that consideration could happen at the next meeting, perhaps, or two meetings. If this report can be ready in a few months, then at that time that question could be addressed.

DR. WALLACE: If the NCSS wishes the working group to address that question.

DR. MacGREGOR: Right.

DR. DOULL: But if your working group spells out a data gap and says that the lack of animal kinetics for troponins in animals, for example, is really needed in order to support the weight-of-evidence conclusion that this is the way to go, there's no problem with the subcommittee supporting the science of that, the fact that that's good science and it's needed, in fact.

But if the subcommittee has an obligation also to help you develop some sort of procedure

whereby you're going to get that information, then I think that's something that we need to give some thought to because we haven't figured out exactly how best we can do that. And that may depend on the discussion we have today.

DR. WALLACE: I would urge you to begin giving some thought to that now, at least in private, because--

DR. DOULL: I will.

DR. WALLACE: It's a definite gap.

DR. DOULL: Other comments?

[No response.]

DR. DOULL: Well, I thank you. We're a few minutes early for our break, but why don't we go ahead and take a break.

We'll go ahead and stick with the schedule. The schedule calls for coming back at 3:15 to deal with the administrative issues, and we'll stick with that.

[Recess.]

x DR. DOULL: Well, as we mentioned in the previous discussion, we're now scheduled to consider the administrative oversight of the NCSS Subcommittee of the Advisory Committee on Pharmaceutical Sciences, and Dr. MacGregor is going

to start us off with a brief resum.

DR. MacGREGOR: I'll be brief because everyone should have received the briefing document in their packets, and this idea has been, I believe, introduced for brief discussion previously.

FDA, in considering where this subcommittee has gone and the direction it's taken, has had a number of internal meetings and reached the conclusion that it would make sense for the oversight of the subcommittee to move to the NCTR, National Center for Toxicological Research, Science Advisory Board.

The rationale is set forth in the document that you received, but basically it is that NCTR has the mandate and the structure to lead safety research, and that's the direction that this subcommittee has taken.

The general structure of the ACPS is undergoing some revision, and Helen Winkle will be speaking to that in just a moment. But basically the ACPS is being restructured along four disciplinary lines in a way that will focus principally on regulatory implementation. And it's felt that appropriate linkage between these two

groups should really be the optimal to optimize the research and the regulatory implementation through these two groups. And a lesser but other consideration is that NCTR is also in a position to coordinate adoption of new methodologies that may arise out of the activities of the subcommittee through ICCVAM and OECD processes, which NCTR has the oversight function for in FDA.

So, as you all know, the NCSS, the objectives are to recommend scientific approaches to improve nonclinical drug development and, in particular, to focus on the predictivity of nonclinical tests for human outcomes and the linkage between nonclinical and clinical studies and to facilitate these approaches through identification of collaborations that could advance the scientific basis of drug development and regulation.

So NCSS really is envisioned and has been operating as a means to capitalize on scientific opportunities with a focus on research needs and collaborative research implementation through processes that you're well aware of as members of this committee. And just to illustrate the vision for the new recommended structure, the key linkages

are shown in this document, the idea being that the focus on safety research would move to the NCTR, which is the center with the main focus on safety research, and that the subcommittee would operate essentially in the way that it has been operating, with input from the public, government, academia, and industry sectors, as well as input from the centers on priorities through the parent Science Advisory Board, as well as a close interaction with the ACPS. And the idea here, again, is that the ACPS will contain these four disciplinary sub-groups with a pharm/tox group that's focused on looking at the science of regulation and how to implement the application to regulatory issues; whereas, the NCSS would focus on collaborative research to identify the areas where science could be used to basically bring it to a point where it's ready for those regulatory implementations.

Now, this was discussed recently at the NCTR Science Advisory Board, and I'm going to ask Dan Casciano to comment on that discussion, and then Helen Winkle to discuss the proposed new ACPS structure and the proposed linkages.

DR. CASCIANO: Thanks, Jim.

As Jim mentioned, in early August there

was a presentation by Jim and Ken and John Doull and Bill Kerns regarding the structure of the NCSS Expert Working Group and the NCSS, as well as the potential of the Science Advisory Board of the NCTR taking oversight of the NCSS. And the discussion was very much like the discussion was just before we broke where there was some discussion regarding implementation and the process of what their role would be.

So there are two concerns. They were somewhat concerned about their role, what their role would be, and they asked for a more detailed road map of what that role would be, and I think that's a similar discussion that we've just had.

They were also concerned by the fact that there was no cardiotox expertise on our Science Advisory Board, and there's also none at the NCTR. And they had some concern about accepting the recommendations of the EWG without prior evaluations by them.

They also--and maybe we can have this discussion here. I think we tried to get at it earlier. How do we implement the recommendations of the EWG and the NCSS committee? So the final result was that they would accept--they would

conditionally accept oversight of the committee, and it would be conditional upon a clearer road map on what their role would be.

I'd be open to questions if there are any questions.

DR. DOULL: Well, why don't we go ahead and have Helen comment. She's the Acting Director of CDER.

MS. WINKLE: Just the Acting Director of the Office of Pharmaceutical Science. I appreciate the raise.

[Laughter.]

MS. WINKLE: First of all, I appreciate the opportunity to come and talk to you all again on this subject. I think that it's really important to come up with some resolution as to how we're going to move forward. I know it's very unfair for you all to be in limbo, and I think, you know, Dan and Jim and I all want to see this rectified so we can move forward.

Unfortunately, there's probably nothing worse than being caught in the middle of a transition, and basically that's where you are. In the Office of Pharmaceutical Science, we are transitioning our Advisory Committee for

Pharmaceutical Science in a different direction than it was originally when it was set up with this subcommittee and several other subcommittees under it.

So what we're trying to do, because of the work that has been done by the two Expert Working Groups--and I think that we'll all agree that that work has a lot of potential for us in CDER as we move ahead. I think it's really important that we come to some conclusions on how we're going to move ahead. And I know that Dan and Jim have been working very hard with NCTR to resolve this problem, and we in CDER have been trying to figure out how to best set up linkages, et cetera, that we can ensure that we can continue to communicate on these areas, continue to work together.

I want to start off with the first slide basically and just reiterate a little bit again what the role of the Advisory Committee for Pharmaceutical Science is.

Basically, this Advisory Committee was originally set up to handle various issues in the generic drugs area, but we found that it was a very good vehicle for bringing folks together and looking at scientific issues, and so we decided to

expand it to take on the whole area of pharmaceutical science that resides in the office.

The problem is, as we took on more areas, we began to have a little harder time identifying what our role was, and it got a little murkier. So basically, though, the role of that Advisory Committee is to have science advisors to help, experts in the area. I mean, we don't have experts in every area, obviously, that we regulate, but to have experts to address scientific and technical issues and questions.

They represent a number of different scientific disciplines that are involved in OPS' regulatory decisionmaking processes. Jim had a few on his slide that showed--but it's a variety of disciplines: clinical pharmacology, pharmacology, toxicology, microbiology, just to name a few. And so there's--and chemistry. So there's a lot of areas. We only have like 12 or 13 people on our Advisory Committee, so obviously, you have--you know, you bring a question on chemistry, you may have two people at the table that are experts in chemistry. So it's very diverse, and so it has been difficult for us to get directly to the type of recommendations that we need on specific issues.

So that's one of the reasons we're in transition, and I'll talk a little bit more about that.

Also, the committee is charged with providing recommendations to help in the development of our regulatory policies within OPS and also in some of the rest of the centers and helping us develop standards. So that's really the main focus, is answering the questions so that we can come up with good regulatory policy and standards.

Next slide?

As I said at the very beginning when this committee was formed, or at least expanded, the Nonclinical Studies Subcommittee fit very well into that current paradigm. It became a subcommittee under ACPS with Jim's help. It was basically set up to develop recommendations on drug development and on approaches in the nonclinical area, which I think we have definitely--the Expert Working Groups have been doing. But, again, being in transition, that has become a little murkier, I'm sure, to all of you as to where that fits into the Advisory Committee. And I know several of you have come to the Advisory Committee. Sometimes the interest is

not as much as I think we'd like to see because we'd like them to take--you know, have a role in this committee. But that has not been the focus, so it's very difficult.

Basically, though, NCSS, too, was charged to identify areas where research is needed to solve problems--and I did change the tense of the verb because I think we're still in that process of determining what research is needed--and to foster scientific collaboration in those targeted areas where we're doing research. That was basically the role of NCSS when it was set up.

You can see there's now sort of, as the transition has taken place, a little bit more disconnect between what NCSS was charged to do and where the Advisory Committee is going. So let's talk about the proposed structure of the Advisory Committee just a second.

Basically, as I mentioned before, we've moved more toward having subcommittees under specific scientific disciplines. We're looking at having a CMC-Manufacturing Subcommittee. Manufacturing has become very important right now in the center because of the new GMP initiatives that have recently been undertaken with Dr.

Woodcock as the lead in this area. But even prior to that, we've had a lot of chemistry questions and a lot of manufacturing questions that we needed to bring before the committee, and obviously, as I said, you may have two people there that are experts on a main committee. So we feel like this is a really important area.

We're looking at a Clinical Pharmacology Subcommittee. That subcommittee will actually meet for the first time in October. We're looking at a Microbiology Subcommittee. It's a really important area that we have more and more questions. We have not focused a lot in the area of microbiology. In fact, recently I have taken the Office of Microbiology for New Drugs out of the Office of New Drug Chemistry and moved it up to the level of the Office of Pharmaceutical Science so we can put more focus, come up with more strategic planning on how to look at microbiology in the future. It's one of the main areas for recalls in pharmaceuticals, and so obviously there's some disconnects there. We need to focus on it.

Another subcommittee that we want to set up is Pharmacology and Toxicology. Again, this is the committee we see running parallel to what is

being done by the NCSS, but this committee would be basically charged with looking at specific science issues, not the resolution on how to get there but identifying some of the issues. Some of the issues will come out of the regulatory area, but also identifying some of the other areas we need to focus on and giving us some recommendations for what we may want to do, and that's a variety of things.

So moving on to the next slide, basically establishing the Pharm/Tox Committee. This is the one committee I know that, again, will have the linkages to NCSS. I know this is really important as NCTR and the Expert Working Groups move forward, how those linkages will be, because I think it's very important that what we do in the working groups, regardless if it's these two working groups we have now under NCSS or future working groups, we want to be certain that the information to come out of those groups finds its way back into the regulatory arena of CDER and can be applied, the findings of the research applied to the regulatory decisionmaking.

So we are in a process of setting up the subcommittee. We are in the process of looking for

a Chair, and we will have approximately five or six members to this subcommittee to start with, to begin to address specific issues. The way the subcommittee system works, we'll have two members from the Advisory Committee itself, and we're looking for members who have strong pharm/tox background. I know one of the new members we have is mainly in toxicology. One of the other members, I think, it's one of the disciplines that he too has some background in. So those are who we will look at to populate as members from the ACPS on this subcommittee.

Then what we plan to do is to address specific scientific questions to the subcommittee once they're established that will arise in the review process. And basically what I see is that this subcommittee should meet for the first time, I'm hoping in February or March. I would have had it meeting as early as October, but I have two other subcommittees that are starting up, and so it's just very difficult to get a third one going, too, in October. But as I said, I hope to go in February or March. I can identify the members by then, get the committee together, and talk about the types of things we want to address with that

committee.

Basically, you know, I see the information that's coming out of these working groups going back into this subcommittee. I think there are other questions that will come along in the regulatory review divisions that will also be important to bring questions to the group. And I've had lengthy discussions with both John Jenkins and with Bob Osterberg, who's currently in the Office of Toxicology under John, about this subcommittee. They're both very favorable for having it set up. They understand the need for the linkages with NCTR, and they also understand the need to bring more expertise into the toxicology area through the subcommittee.

Next slide?

As I said, I see this subcommittee discussing questions, making recommendations back to the main committee, basically either coming directly with an answer on a specific question or on what additional information is required, whether it be research, whatever, to answer the question; and then to provide follow-up on questions. Of course, all questions often lead to more questions, so this committee would be then charged with doing

that.

Next slide?

The important thing, though, here, I think, is the linkages to NCSS, and I think this is what's on most people's mind as they think for where we're going in the future. And, again, I know these two Expert Working Groups have put a lot of effort in coming up with recommendations, and I think it's up to Dan and I and Jim to make sure that we continue to move forward in this area.

But the connections are important, not only with the two groups we have but with future groups. We need to be sure that the connections are there between review and research. This is a problem that we have continuously in the center. I don't think that's anything that needs to be hidden, and it takes more work, therefore, to make sure that the connections are there.

We'd want a member of the NCSS on our Pharm/Tox Subcommittee. I think this is really important for the exchange of information, the exchange on data. We also want a member of our PTCC Research Subcommittee on the NCSS. Again, this back-and-forth involvement with both groups. So it's going to mean some work for whoever is

on--for one person on each one of these committees, a little extra work. But I think that linkage is very important.

The NCSS would independently identify areas of concern which it could bring before the subcommittee. So what we would like to be able to do is either have the member from the NCSS Committee--now, this is, of course, if it moves to NCTR--be able to come into our Research Subcommittee and talk about areas of concern, things that have been recognized in their working groups and bring it before the subcommittee, or vice versa, the subcommittee could then go and talk with NCTR and NCSS and begin to, you know, work out future direction for questions or areas of concern in the regulatory area, and the Pharm/Tox Subcommittee could identify perceived research needs, too, again, in discussion of the problems, either at the subcommittee level or even at the Advisory Committee level, and bring those issues and concerns to the NCSS. So we see that as a very good way to remain--to continue with the linkages, but we also feel that these linkages are extremely important as we move ahead.

I don't think they can be done currently

as we're set up with the NCSS as part of the Advisory Committee, again, because of the transition. But I think this is an excellent resolution to that.

So I'm open to questions.

DR. DOULL: Jack?

DR. REYNOLDS: Just one question, Helen. On the Pharm/Tox Subcommittee that you're forming, will you have industry representation on that committee?

MS. WINKLE: Yes, we will plan on industry representation. This is the one thing that's really been good about the subcommittees, is we have had industry membership there. It's especially been helpful. In our current Process Analytical Technologies Subcommittee, we have a number of industry folks there who are providing us with their expertise, their knowledge, et cetera. So, yes, I would plan to do the same thing here as well.

DR. DOULL: Let's take a hypothetical. Let's assume that the Cardiotoxicity Working Group puts together a recommendation about use of troponin and it envisions the need for a study to provide--to fill the data gaps and so on, and then

makes that recommendation and the NCSS approves that and it gets that level of peer review.

Then I guess if that were an NCTR, then that recommendation would come to your Science Advisory Panel who would look at that recommendation for its science quality?

DR. CASCIANO: Yes, they would look at it for the science, also how it fits into our other--the other priorities that are ongoing at the NCTR and what kind of expertise would be required to monitor that kind of activity and how important that was to the agency. And the importance of that subject to the agency would bubble up the priority as far as the NCTR is concerned.

We respond to five product centers and not just to the Center for Drugs, and each one of them thinks we work for them. So it's difficult to come to grips with setting priorities, but we generally do without too much difficulty. And it depends upon what the subject matter is. Someone would have to develop and design the experiment, write the protocol and determine the kinds of biomarkers that would be evident. And if the expertise didn't exist at the NCTR, then we somehow would have to obtain resources to develop that expertise.

DR. DOULL: I guess I--

DR. CASCIANO: Excuse me, and that could be done through establishment of interaction between the Center Director from Drugs and the NCTR. So it's possible.

DR. DOULL: I'm thinking mechanics somewhat. You know, if, for example, the study was needed and it was a study that was of great interest to industry and Food and Drug had some interest in it and so on, then theoretically one could have a joint kind of effort in which there would be a protocol developed and approved, say, by the Science Advisory Board, whatever, and then funding would be sought, you know, from industry or ILSI or government or whatever to get this study done.

I guess the procedure for that then--there's on problem with the procedure for that, if that were all developed and approved by the Science Advisory Board?

DR. CASCIANO: No, there are no difficulties with that. As far as if you're asking conflict of interest potential, we have mechanisms to develop cooperative research and development agreements as well as other mechanisms for carrying

out work. In fact, we've done--we had cooperative research and development agreements with Astra-Zeneca, so this is a regulated industry.

DR. DOULL: I guess the only reason I bring that up is, you know, that was one of the things that was attractive, I think, to our subcommittee, is that we felt the Advisory Committee was focused mainly on regulation and the NCSS really was focused more on research. And, therefore, we needed a mechanism whereby our research would be evaluated by a science advisory group and that it would be facilitated, whatever plans were needed to get that research done.

DR. CASCIANO: Right. We have several mechanisms at the NCTR for research evaluation. As you know, we have a large interaction with the NIEHS through the National Toxicology Program, and we have a toxicology study group that's associated with just that part of our efforts. And that's separate from our Science Advisory Board.

And the Science Advisory Board meets on an annual--the process is that the board meets on an annual basis, and we evaluate status and the Science Advisory Board votes on recommendations by subcommittees of that Science Advisory Board. We

use the NIH site visit concept, so each program is site-visited every three or four years by a subcommittee of the Science Advisory Board, and that's how the peer review takes place.

MS. WINKLE: I think, John, you make a good point, too. I think as you said, the Advisory Committee seems to be more focused on the regulatory, where the NCSS is more focused on the research. But I think this is where really the beauty of having the two committees is, and that's the fact that once the research is completed, it can come back in, the data that comes out of the research can come back into the subcommittee, the Toxicology Subcommittee, and the Advisory Committee and basically help set some of the bases for the regulatory decisions that are being made or setting those standards and policies. So I think that that's a really good mix.

DR. CASCIANO: And just to get a little more detail, we'd be very interested in the -omics(?) application to these efforts because we are developing an integrated -omics approach from micro-ray to pereomics (?) and metabonomics (?). And we have extremely unique animal facilities so that we can apply these to a specific question, and

the question can either be a primary question or a primary--whether toxicity is primary or secondary, where the kidney is and cardio is secondary, and perhaps we can weed this out using the tools of the new technologies. We have interest in it.

DR. DOULL: I think in Dr. Wallace's presentation he didn't mention -omics much, although they've talked about it because they focused on troponins. But tomorrow you'll hear from Dr. Kerns, and -omics is certainly high on their list of potential candidates.

Dr. Green?

DR. GREEN: Just one question for Helen. Maybe you could comment on the kind of topics that the Advisory Committee meeting might take on with its subcommittees. Would these be topic-specific or product-specific, or it depends?

MS. WINKLE: They would be topic-specific. Most of the issues that we bring before our Advisory Committee are very general. They're not on any kind of specific product.

What I see--and, actually, Frank may be able to talk even more to this because there are a lot of examples that have come up in the Pharm/Tox Coordinating Committee within the center. These

are the types of issues that would be brought forward.

So basically I see, too, some things that are being done through the working groups brought there, too, such as like on determining troponins, what are useful indicators for drug-induced cardiac injury. We could take a look at that data and determine if that data was strong enough to basically support the routine measures for troponins and whether we'd want to add those particular clinical chemical endpoints into tox studies.

I think questions like this, again, based on some of the data we find in some of the working groups we have or future working groups, but I think there are, too, a number of other questions that come up in the tox--general questions that come up in the area of toxicology that we could utilize this committee to address and come up with either some possible answers or possible directions we should be going in to get those answers.

DR. DOULL: Jack?

DR. REYNOLDS: I guess a couple things. One, I thought what is being stated here is actually two separate functions: one focused on

the research, the other focused on regulatory implementation.

I guess for some reason I thought that was what the original NCSS was migrating to or part of the remit was to come to some of those recommendations. So if that's not the case, then I think that there are merits in what I'm hearing, but just to kind of talk about it practically, what I'm hearing is the Nonclinical Studies Subcommittee will now in essence be an extension of your Scientific Advisory Board. And I guess it will be more of a working type of group than what the Science Advisory Board was, and that the Advisory Committee on Pharmaceutical Sciences will then be what I--some of my comments I made earlier around troponin, that this current committee as it's structured I thought should be making recommendations on the merits of a particular biomarker. But apparently that's not in the remit, or at least the current thoughts about the NCSS, but that's what the new Pharm/Tox Subcommittee would be doing is that.

So I think there's a clear need for both of those. I would come back to that and I guess just ask the question of why can't the current NCSS

as it's structured do both of those. Is there some gap in administrative policy or maybe not the right membership or what?

MS. WINKLE: Your questions are very good. I think in some ways that we have focused so much within the subcommittee on these two working groups that the thoughts were that it would probably be better to continue with these working groups and start a committee that had sort of a different agenda, different focus, and could be broader in the scope of what they looked at. Certainly there is some--we could give some thought to taking the current committee and making--do some restructuring around that.

But, again, part of the situation is the difference between the research and the regulatory area, and we were looking for some way to be able to capitalize or take advantage of all the efforts that have been put forth by these two working groups in the research area, to continue to capitalize on that and move it forward. So certainly that is a possibility.

DR. DOULL: Yes, I think, you know, regulatory affairs are the concern of NCSS only after they have gone through the research and

developed whatever it is that they're going to make a recommendation for. And you were on the committee before, so you are--but all of the initial ideas we had really were research-oriented. We wanted to look at PET scanning and see how well we could use that for something, and we'd talk about genomics and where we were at, you know, with all the -omics. And it was a research issue. It really boiled down to a research issue because we weren't far enough along to make a regulatory evaluation of that.

So in that sense, the committee, since I've been with it, has really been research-focused because we're trying to figure out, you know, how good these techniques are, how well they make the right predictions and to develop appropriate biomarkers. And troponins are the closest example we have of one which turns out to have some merit, which maybe could then approach a regulatory one.

I think the suggestion that Helen is making is that, you know, we don't lose the regulatory avenue. We still have the ability, once the research tells us where we ought to be going, to come to the Advisory Pharmaceutical Committee and say, hey, this technique is really worthwhile

and you ought to think about doing a guideline or getting it into the procedure some way.

Jack, you were going to--

DR. DEAN: I had about the same level of confusion Jack had because it strikes me that this committee would now have two subcommittees to report to--or two committees to report to: the SAB for NCTR and this new committee that Helen described. So I'm confused what the remit is now of this committee. It seemed like early on one of the issues in this committee was that we didn't have a vehicle to be able to fill in the research gaps if they were identified, that we would identify the research gaps, but there was no vehicle or funds to fill the gaps. And I think NCTR, if that's the direction, would provide possibly through CRADA (?) the opportunity for industry to come together, pool their resources, and work with government to fill the gaps.

I assume, Dan, from what you've said, that exists.

DR. CASCIANO: Yes, that's viable. And when we initially discussed the movement to the NCTR, this is what we had in mind, was collaboration with industry and with Drugs--to

respond to Drugs' needs.

DR. REYNOLDS: So just to reflect, to me the reason we have focused on science here is that we looked at a number of things that the NCSS could deal with, and for a lot of reasons, we eliminated some. For example, one that I was championing was, in fact, the efficient entry into clinical trials, which, in fact, wasn't research as much as it was adopting standard practice on what were prerequisites to studies in humans and then what would you have to do.

But the reason we focused on science here is because both of the problems were dealing with, the cardiotoxicity as well as the vascular injury, are perplexing issues with regulatory agencies. There were no clear measures of this. There was no clear basis upon with to make regulatory decisions. So, in my view at least, that's why we focused on the science, was to generate the data or the knowledge for which one could then make regulatory decisions. So that's certainly what my mindset is there. But what we're saying now is that we're going to essentially separate the two. One, we will have the science advisory thing, an extension of the Scientific Advisory Board. Then we have

that group that decides whether these issues or the data or the endpoint are appropriate for regulatory decisionmaking.

So then I come back to the question. I mean, this--NCSS has had difficulty, I guess, in maintaining a focus and process and how we get things done. I'm a little unclear how then separating the two that have some overlap in their overall objectives, how they would accomplish that when we probably haven't been able to accomplish too much in the last couple years.

MS. WINKLE: Well, I think that you make some good points here. I think the disconnect for us, for the Advisory Committee and NCSS, is, again, the research versus the focus on regulatory review. And basically all of the research or the science has been vetted out before it comes to the Advisory Committee. This is probably one of the few times the Advisory Committee has gotten into trying to develop the science themselves through one mechanism or another. So that's part of the disconnect, and I think that, you know, in original discussions that we had, we felt like if the science could be done through NCTR and then brought back into the Advisory Committee with all of the

information, then they would be in the same position, in a situation where the science was there to help them in making their decisions or recommendations.

So there is a disconnect right now. You know, this was one way that we looked at that we could solve that disconnect.

DR. CASCIANO: It was a convenient way to solve the disconnect because you just can't develop another Advisory Committee, and the NCTR's Advisory Committee was in place, and this would attempt to handle the transition. And we have interest--and the NCTR is interested in supporting FDA high-priority needs.

DR. SELKIRK: Can you give us some idea how the--logistically how things will transcend, that is, the ideas and issues will transcend down through the NCSS to the Tox Subcommittee for work and then work its way back up? Or will it come down from NCTR directly? I'm just curious how the issues will move their way through the system.

MS. WINKLE: I think it will work both ways. This is what I would hope. I think there will be areas where NCSS and NCTR would recognize areas that they thought needed more vetting or

regulatory questions that they felt like needed something and would make suggestions and we could discuss those at the Advisory Committee and then determine what direction we want to go and make recommendations back down to NCTR and NCSS, or vice versa.

I'm hoping that the questions will come out of our regulatory review staff into the Advisory Committee, and then we can work with NCSS on areas that we can resolve.

Again, though, NCTR is going to have to prioritize some of these things, just like the center is going to have to prioritize. There's only so many directions that we can go, so many directions that we could continue to support. So we'll have to work very closely with NCTR.

You know, from my past history with NCTR, actually this is a very good linkage that we haven't had in the past. I would say--and Dan can certainly agree or disagree--it's been more an ad hoc basis where we've made these connections. I think these two committees give us this formal, now, process in which we can work more closely together in this area.

DR. CASCIANO: Well, I agree, Helen. Our

previous interactions were generally through the National Toxicology Program, and that was one mechanism for interaction. But this one seems more scientific, more basic in nature, and the other partner in developing the concepts is the committee that Frank is a part of, and I don't--are you leaving that committee, the PTCC?

DR. SISTARE: Research Subcommittee. I co-chair that with the Chair of the--

DR. CASCIANO: Well, there will be input from that group as well in identifying regulatory needs that would come to this group, and I guess this is how the cardio came to this group. And we would be involved initially with that group in helping develop the concepts that would come to this group.

Is that your thinking process?

DR. SISTARE: Yes. The other thing is an interesting way possibly of looking at it is sort of like a system of checks and balances where you have one group that's gotten very vested in developing a product, getting it to a certain point of maturity. It's hard to dissociate yourself from that once you've gotten it. You want to make it succeed because you put so much effort into it. So

it's almost, you know, logical to have an independent body on the other side of the fence you can dish it off to and say, here, take a look at this, this is all fresh and new to you. You're going to take a much more objective look at it now. And you've got, you know, some experience with respect to the regulatory arena: We think that this is ripe now for regulatory practice, what do you think? And they have another perspective.

So, in a sense, you kind of look at it that way, by having the division between the people that are really invested in making sure the research is done right, gaps are identified, gaps are filled where needed, and then the other group that's got to integrate it in practice to sort of take another fresh and independent sort of look at it. So that's another way of looking at it.

Also, in terms of the process, you could probably start in a number of different places, but if we take as an example where we are right now with the troponins or the vascular injury stuff, as Dan pointed out, those issues, along with several others, came out of the PTCC Research Subcommittee. These were identified as big problems, some that our own labs in CDER were working on at the time,

but yet clearly we're not going to be able to solve in and of our own efforts. You know, it's going to take publishing it out there and then having someone else pick up on it, try to get others--this is a way of getting the whole thing orchestrated and getting it to a point of maturity where we could really get it into practice quicker.

So I could see there would be examples of things like that where CDER sees issues that come up in review that are never really satisfactorily addressed, but you've got to make a decision right here and now. You've got to come to a certain level of comfort, and you make a decision here and now and then you forget about it, you go on. It comes up again in another review division. You've got to make a decision, you do it, but you never really evolve, you never really change things.

But by having a group that's focused on those common things that keep coming up time and time again, different review divisions that have to be abandoned, you have to leave them. But if you've got someone thinking about research and saying here's a way we can make things better, bring it to this Advisory Committee, you know, within CDER and say, you know, we're seeing this

problem time and time and time again, what do you think?

So, you know, yeah, you're right. We need to get this solved. We dish it off to the NCSS and say, you know, our regulatory center is seeing this with a certain amount of frequency, it's got to be dealt with, can you guys come up with a research strategy to help solve it? They do that. NCTR is really geared toward research oversight, and that's part of, I think, where the difficulty comes in. In a perfect world, you've got research and review all happening all at the same time and everything is commingled. But in reality, CDER is really geared toward, you know, making decisions here and now on products, and you've got to make a decision. Is this ready to go into clinical trials? Is this ready for product approval, et cetera, et cetera? NCTR is really geared toward a research process.

So we're going to do what we do best, and they're going to do what they do best. And I think that's what we're trying to do, is we're trying to take advantage of those two and set up a committee structure that integrates those two stovepipe matrices in a sense.

There's no perfect solution, but I think

this is a good one.

DR. DOULL: One option would be to say we don't need NCSS. We could simply, as Jack suggests, hand that off. But the danger in doing that is that we would lose the link to ACPS. And I don't know by just having a member on the Pharm/Tox Committee whether that would be a real enough link. That link is important when you finally get to the stage where you really want to impact the regulatory process, and if we lost that, then, you know, you would have to deal with--in the same way you deal with the other five product groups in a sense. This is kind of a useful tool to get to it. But it may not be the best tool, and I don't know that there are other ways that one could do that.

However it would be done, it must maintain that link to the regulatory process because, bottom line, that's really why we're all here, is to figure out better ways to regulate new--in the introduced new drugs and see that they get properly regulated.

MS. WINKLE: I agree, Dr. Doull. There are probably other ways to do this, but what's happening is we're continuing--we're not moving forward because we're sort of wrestling with how

best to do this. And I think, you know, that Dan and I sort of pledged to help make this work, and I think it would be good if we could move in this direction and put the effort we have to put into making it work. I mean, I think whatever direction you go, whatever model you choose, you're going to have to put some efforts into it. And I think since this model is matured in our minds, at least, we ought to go ahead and move forward, because if we don't it's holding up what's happening in these working groups, and it's holding up other issues from having the proper forum for introduction.

So I really feel that we need to sort of move ahead now.

DR. CASCIANO: Well, I just want to confirm that we're committed to it as well, and we're just interested in how we can develop the best process so that we all can provide what we think is needed by the new regulatory agency.

DR. GREEN: I just had a couple other questions regarding your thoughts on the role of the new Pharm/Tox Committee. And as Dr. Sistare indicated, I think the day-to-day pressures essentially of just getting the work done, sometimes a decision has to be made, and it's made

under the best available data set in this division, and we all know that occurrence is perhaps the same circumstances or data set in another division may be a different decision, and I think that is one of the issues that amongst the PhRMA Drug Safety Steering Committee we often here commented upon that there's an inconsistency of seemingly the same decision being made across different areas of the agency.

Now, particularly in areas where we're dealing with regulatory decisions on perhaps a new biomarker and the significance of this kind of a decision to make a go/no-go decision, or to perhaps address a level of concern, do you envision that this would be the kind of issue that this Pharm/Tox group would make a decision on, that this is ready, this is not ready, and take responsibility for communicating how this data set should be treated throughout the CDER divisions?

MS. WINKLE: Yes, except for the fact that the Advisory Committee doesn't make decisions, it makes recommendations to the agency. So what the agency would do is go to the subcommittee basically try to take advantage of the expertise, their knowledge in the area, their experience in the

area, take all of that information along with the internal information within the center, and based on the Advisory Committee's recommendations as well as what's internally within the center, make some decision then as to what you want to do as far as the regulatory policies or standards are concerned.

The one thing is if in talking to the experts out there, there was a determination that we didn't have enough data, that enough data didn't currently exist on which to make that decision, that's when we'd look toward NCSS, NCTR to help in getting that data.

DR. GREEN: One follow-up to that. What piqued my interest was your comment about the establishment of the CMC-Manufacturing Committee to deal with, in addition to many other issues, the new GMP initiatives. In particular, when we're dealing about applying new technologies to standards that might historically--that we've been dealing with for the last 20 years for safety assessment data, these by some are thought to be needed to be conducted at a certain level, and that baseline level where most of these studies are conducted is in compliance with good laboratory practice regulations.

When you start now talking about the introduction of a new test, a new system, a new assay, a new technology, oftentimes it's very confusing to those of us in industry with respect to what standard they're expected to be held to, good science aside. Is this also kind of a topic that might be taken to this committee for clarification, advice back to the reviewing divisions?

MS. WINKLE: Is this for the CMC Committee?

DR. GREEN: Well, for--

MS. WINKLE: For any of these subcommittees.

DR. GREEN: Right.

MS. WINKLE: Yes. I think the issues will vary, but obviously there will be advice on--recently we looked at blend uniformity as to whether we should continue standard blend uniformity testing or discontinue it and use stratified sampling instead. I see more general questions like that being addressed to the committee, and there's where we have done the research--or the research had actually been done by the Product Quality Research Institute and brought

forward to the group.

So this is the kind of information that I think--I don't think that the group is going to make recommendations that you need a certain test to be done. It's more looking at the tests that are done and making the decision whether they had any value to the actual regulatory decisionmaking. It will be more general, I'm saying.

Does that answer your question?

DR. GREEN: Yeah, I think that what I might do is just be clear on this point because it has to do with the application of the laboratory practice regulations or the expectation of those applications to new technologies. And it would be very important, I think, that members or a representative number of members of that committee realize what the implications of complying to that standard, what that really infers, because a simple comment, yes, we expect this to be done to a certain standard triggers a whole level of activity within sponsor--within industry laboratories that really might not reflect the intent if this individual knew what, in fact, those regulations--or how they impacted how things are done. So that would be one concern that I would

have, particularly around the new technologies and the ability of industry to adopt them and apply them.

MS. WINKLE: One thing that's very helpful for the Advisory Committee is, of course, these are open public meetings. And there are often various groups that come in and speak or representatives from industry, you know, a specific industry that will come in and speak. So it's very open to being able to vet the issues from a variety of different directions. And one of the things we've tried to do, at the Advisory Committee level, anyway, is bring in experts who have various opinions on particular processes, et cetera, so that those opinions can be vetted and discussed before any kind of recommendation is made.

So, no, you have a very good point. It's certainly something that we're very much aware of the need to be certain that the directions we go in are helpful to everyone concerned.

DR. DOULL: Jack?

DR. REYNOLDS: Mr. Chairman, are we going to vote on this, or are you going to go around and ask us what we think about this? I'm a little unclear where we're going with this. And when I

find that out, I might offer some comments.

DR. DOULL: The recommendation that the home of the NCSS be moved from ACPS to NCTR was made sometime ago and has been suggested to your Science Advisory Committee who has considered that. So the decision is not the NCSS. It is the decision of whoever created this committee. Jim, who created--it was created as a subcommittee at ACPS.

DR. MacGREGOR: Ultimately, the decision to constitute these committees is an FDA decision as to how they'll be constituted. I think the point here is that I think we all want all of the individual working groups to be comfortable with what's being proposed and want to get a reading on that to make sure that mistakes aren't being made in the view of the people on the committee.

DR. DOULL: You know, it is important that the NCSS, in fact, be aware of the change that's occurring and be comfortable with that change. And I guess, you know, it would perhaps be useful if the NCSS committee members, in fact, did say they felt this was a good idea.

I would simply say for myself, one thing that NCSS has, in fact, done is to look out there

throughout the field for good biomarkers in all sorts of areas and to decide which ones could be mined most profitably right at the moment, and that's why we've delayed on some and accepted others. So if that committee vanishes, then somebody else has to take up that task of figuring out where the next best biomarkers are going to come from. So I think--and this arrangement seems like an arrangement that would preserve that activity and would maintain the regulatory link.

So, from my point of view, I think it's a useful sort of thing. But you guys are members. What do you think? Do you think--

DR. REYNOLDS: Well, I guess that's an invite to give my opinion. I think one of the things that the current NCSS structure has struggled with a little bit is kind of what we talked about today. So we've seen evidence in the outline, but I know the Expert Working Group has a lot more data that they would incorporate into the documents, that we have a very good biomarker here for cardiotoxicity. And some of my comments earlier were, then, so how do we get that into a regulatory practice? I think the current NCSS has struggled with that.

What I see in terms of the proposal to me makes a lot of sense because it really does separate the data gaps, the research to fill those gaps, and the ability to create collaborations with all stakeholders, including industry, under a sanctity group that really focuses on safety sciences as their business and then being able to take that back to recommendations to divisions that make decisions about the merits of endpoints and the merits of data.

I think there's--I mean, based on, I guess, the--I don't want to say lack of inertia in a negative way, but I think our inability to get to incorporation of some of these things into regulatory practice, I see the current proposal as, I think, a really good way to get there. So I'm tending to see this favorably, what's being proposed here.

DR. DOULL: Jack, you're a member. Do you have an opinion on this?

DR. DEAN: I would echo what Jack said and take a slightly different approach. I think one of the comments that Frank made earlier that I was quite impressed with, anytime we look at technology and data, we always find data gaps, and the problem

with that is always how you fill the data gaps. And with the current structure I don't think we really have a vehicle to do that, and I'll take the ILSI model where industry comes together with government and academic people and does collaborative work to fill data gaps and to look at the direction of the safety science.

I think that NCTR might also provide that kind of a vehicle through their CRADA(?) and through their scientists. So it could be a very rich collaboration, I think. So I'm very positive.

DR. DOULL: Good. Gloria?

DR. ANDERSON: I don't have any objection to it. It seems to make perfectly good sense to me. I do have a question, Jim, about this sheet right here, your presentation, the linkages on that sheet. I've been sitting here trying to figure out the PTCC Research Subcommittee. Is that the same as the other one over there?

DR. MacGREGOR: Probably Frank Sistare, who is co-Chair of that, could comment on it and its role.

DR. ANDERSON: Okay.

DR. SISTARE: The PTCC Research Subcommittee is made up of an equal number of CDER

research, laboratory research principal investigators and individuals from each of the offices within the Center for Drug Evaluation and Research that are focused on review in the pharm/tox arena. So that is a subcommittee that is totally internal FDA. We're dealing with proprietary questions, proprietary issues. It's not in the public domain at all. It's a very private internal group, and we are involved in review of our own internal research to make sure that, you know, what we are proposing to do is perceived as high priority and are there other issues that are resurfacing in a--like I was saying, you know, common questions that keep coming up across different review divisions: You know, why drugs are being put on hold? You know, is there a question there? What's the science that's lacking when we see certain consistencies coming up? And are there things that we need to solicit NCTR's help on? Are there compounds, old compounds that may need to be tested for carcinogenicity?

There's a whole gamut of things that we deal with--repro(?) tox--that we deal with in terms of prioritizing and finding a vehicle to get the questions answered and to get the research done in

some way. But it's a very internal group.

This other group over here under ACPS, that now is your external Advisory Committee for Pharmaceutical Science, and underneath there, Helen is proposing that a Pharm/Tox Committee be set up. Again, those would be external, non-CDER personnel that would be there, much like yourself and other people in academics and, as pointed out, a certain number could be from industry as well.

So those would be the experts that we would go to for consult.

DR. ANDERSON: So what is the relationship, then, between the PTCC and the Pharm/Tox? Would they--I guess where I'm confused is that I think there are probably some other subcommittees that interact with the other advisory committees. From this chart, it seems as if that this particular subcommittee is saying to CDER--telling CDER whatever it should tell CDER for ACPS, and the Pharm/Tox people, I don't know where they fit into that. Am I making myself clear?

DR. SISTARE: Perfectly clear. I really think the arrow--and I really shouldn't speak to the diagram. It's Jim diagram. But I really think that the dialogue is going to--

DR. ANDERSON: I always have trouble with these equilibrium reactions.

DR. SISTARE: Right. The arrow of discussion is probably going to be directly between the PTCC Research Subcommittee and the Pharm/Tox Subcommittee of the ACPS. That's really where the arrows are going to go.

DR. ANDERSON: Okay. I understand.

DR. SISTARE: And also from the Pharm/Tox Subcommittee of ACPS directly to NCSS, would be my guess, is where a lot of that dialogue is going to go. So some of the arrows may not be accurate. All the boxes are there.

DR. ANDERSON: And the line to the CD--okay. I understand now.

DR. DOULL: When we discussed this previously at our last meeting, the subcommittee, NCSS, said that in going to NCTR that we should say that the subcommittee thought--reacted favorably to that and should explore it. And I think now we're in the position where we would say, well, we have explored that, and the subcommittee, the NCSS Subcommittee, feels comfortable with it and endorses it, which we would say, then, I guess, to the Science Advisory Board, your Science Advisory

Board, that it comes with the recommendation of our subcommittee, and we'll try and figure out how best to make it work to be a win-win situation for NCTR and for ACPS.

Jim, you were involved in this from the beginning. Do you think we're going in the right direction?

DR. MacGREGOR: Yeah, I think we're going in a profitable direction.

DR. DOULL: Any other final comments? Have we solved the problem for Ken and for Bill tomorrow? We'll come back and discuss where this puts us in regard to the research to fill the data gaps.

DR. KERNS: Maybe I could just make a comment. I think having chaired this group with Les, my colleague from GSK, whom I should have announced this morning, but he's here in spirit, I think our greatest frustration over the past 18 months is trying to--it's not really identifying the gaps--the gaps are obvious, and, you know, filling them--and putting everything down on paper, but it's coming up with solutions as to how we can implement the research programs necessary to bring real new data to the table that will help the

regulatory--the authorities. And I think if this--moving to NCTR I think is also a step in the right direction. I don't know if it's the ultimate solution, but it's a step in the right direction, and I think it will provide us with an opportunity, I think, to access the appropriate resources, either internal or external to NCTR through CRADA, as Dan mentioned, to bring solutions to the table and do the research that's been identified in the gap analysis. I support it.

DR. DOULL: Any final comments?

[No response.]

DR. DOULL: Tomorrow morning we meet at 8 o'clock, and tomorrow morning we'll spend the morning dealing with the Vascular Working Group results.

MS. REEDY: You may leave your materials on the table if you like, and there will be a shuttle service. Jim has offered a shuttle service to the hotel. Is that right?

DR. MacGREGOR: I have a car, and I'll be happy to make as many trips as we need to do.

[Laughter.]

DR. MacGREGOR: How many people need to get to the hotel? Six. So I'll offer that. It's

a convenient walk, and I'll be happy to make two trips. So why don't we, just those of you who would like rides stay? Can I just ask, though, did we settle on a time to meet for dinner? Do we need to agree on a time at the restaurant?

MS. REEDY: Five o'clock in the lobby of your hotel or 5:15 at the restaurant, which is a block north.

DR. MacGREGOR: Okay. Is that okay with everybody that was going to go? Any problem for anyone?

[No response.]

DR. MacGREGOR: Okay. So if anyone doesn't know where the restaurant is, it's just, as Kathleen said, one block north of the Double Tree on Rockville Pike. Okay. So those who would like a ride just remain here and see me.

[Whereupon, at 4:27 p.m., the meeting was adjourned.]

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