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CENTER FOR DRUG EVALUATION AND RESEARCH

NONCLINICAL STUDIES SUBCOMMITTEE OF THE ADVISORY COMMITTEE FOR PHARMACEUTICAL SCIENCE

VOLUME II

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C O N T E N T S

P R O C E E D I N G S

Welcome and Introductions

DR. DOULL: Let me welcome you all again to the second day of the meeting of the Nonclinical Studies Subcommittee. We're a subcommittee of the Advisory Committee for Pharmaceutical Sciences.

And yesterday we heard from Dr. Wallace. He presented the achievements of the working group—the Cardiovascular Working Group—and today we're going to hear from our other working group, and that's the Working Group on Vascular Injury.

Okay. We'll do all these official things.

I'm John Doull. I'm a Clinical Toxicologist from KU. Gloria?

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

DR. CAVAGNARO: Joy Cavagnaro. And I'm on the committee as a representative from Bio.

DR. WALLACE: Ken Wallace, University of Minnesota, Department of Biochemistry and Molecular Biology, and I chair the expert working group on drug induced cardiac toxicity.

DR. KERNS: Good morning. Bill Kerns. I'm from PhRMA Consulting in Boston, and I co-chair the vascular injury expert working group.

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

DR. MacGREGOR: I'm Jim MacGregor from the National Center for Toxicological Research, FDA.

DR. GREEN: I'm Jim Green. I'm from Biogen, a toxicologist, and I represent Parma.

DR. SELKIRK: I'm Jim Selkirk. I'm from the National Center for Toxicogenomics, part of the National Institute of Environmental Health Sciences.

DR. CASCIANO: I'm Dan Casciano, of the National Center for Toxicologic Research, FDA.

MS. REEDY: I'm Kathleen Reedy, Executive Secretary of the Advisory Committees and Subcommittees.

Meeting Statement

MS. REEDY: This is our meeting statement for today. If you notice any differences from yesterday, I'll be surprised.

Acknowledgment related to general matters waivers for the Nonclinical Studies Subcommittee of the Advisory Committee for Pharmaceutical Science, September 10, 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 12A30 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 broader 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 may 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.

Introductory Comments

DR. DOULL: Thank you, Kathleen.

Are there any comments on the disclosure?

[No response.]

I have two quick announcements.

The topic that we're going to deal with today—the Vascular Working Group report, was

available, I think—isn't that available to everybody?

MS. REEDY: Yes, it's on the Web.

DR. DOULL: And it's out on the table.

MS. REEDY: And it's out on the table—yes.

DR. DOULL: Okay. So if you don't have a copy of that report, it is available.

I think the subcommittee got it a week or so ago. So they've had a chance to review that.

The other thing is I need to mention that after the break we will have an open public hearing, if there are any public comments. We don't have any formal requests for public comments. But we'll do that after the break.

Do we have any other housekeeping?

Okay. Then why don't we go ahead and proceed with out—Dr. Kerns can tell us about what's happening with the Vascular Working Group.

Bill?

Report of the Vascular Injury Expert Working Group and Subcommittee Discussion of the Report

DR. KERNS: Thank you, John. And thank you to the NCSS for asking Ken and I to come today and yesterday to speak.

I'm here representing the Vascular Injury

Expert Working Group, and our committee is composed of several members that represent industry, academia and government--I think evenly balanced, and a skill set that has brought great value to the document that you see in front of you on the table.

And I want to acknowledge everyone for having contributed to the document. Everyone did a very good job of having it come together.

Importantly, along the way over the past 18 months to two years, we have--several active contributors, as I'm calling them, have joined the committee as ad hoc members, and have made substantial contributions, also, to the document in front of you. And I'd like to recognize these members, as well, on this page, who represent, primarily, industry and I want to also acknowledge Jin Zhang from CDER, who was inadvertently left off of the membership list in the document in front of you.

And to let you know that we've been very busy—this isn't to read, but just to point out that we have been alive for 18 months—close to two years now. And we have met many times on the telephone, face-to-fact, to bring this document to fruition.

Our next planned face-to-face meeting is

at the ACT meeting in Hershey, Pennsylvania in early November.

Today's objectives are to review with you once again our mandate, as we understand it. I want to spend some time describing to you why we think, and we agree, that this is an important issue that requires resolution. I want to review our progress that we've made to date. And, finally, and importantly, a set of slides of discussion points for discussion and feedback from NCSS to the committee.

Our mandate, as stated in the document on the table, as we understood it, was to evaluate and develop a thorough and current understanding of vascular injury issues, both pre-clinically and clinically. We have done this—and it has taken quite some time, to bring the whole committee up to the same level of experience and expertise. Keeping in mind that the committee is populated by many people who had no knowledge of this issue prior to getting together, and that took quite some time.

We're charged also with identifying opportunities for new biomarkers, based on probable mechanisms of action. Important to note here—and I

will show you in some slides, that we don't know mechanism of action, so we're really focused our biomarker search at this point on what we think to be most likely probable mechanisms.

Ultimately, we will develop validation plans to bring the biomarkers to fruition so that they can be used preclinically and clinically. And that is the last two bullets or items that I don't think will actually come to fruition for a couple of years.

So what is the issue? Drug-induced microscopic polyangitis in humans—also known as hypersensitivity angitis, or leukocytoclastic angitis, is not—or certainly rarely, observed in preclinical animal species. This is a fundamental problem. So, in summary, the most common even that occurs in humans with drug-induced vascular injury does not—we do not see in the nonclinical toxicology. It is, however, observed occasionally in clinical veterinary medicine in pet animals, as an adverse event to antibiotics, primarily.

The current animal models are then poor predictors of drug-induced lesions in humans. Because the common drug-induced vascular lesions that we see in animals are "not know"—in quotes—to

occur in humans, and they have unknown relevance. I say they're not known to occur in humans, because we have no way to really look, at this point in time. So we've been moving forward for the past decade—many compounds are on the market, compounds that cause lesions in animals—and thus far there have been no serious related adverse events that we're aware of that occur in humans. But we don't know, because we don't know how to measure.

Equally important, the lesions that we see in animals, induced by drugs, generally occur in vascular beds that are also prone to spontaneous disease. This is important, but I—and I don't think we as a committee—understand clearly what that means. But it must mean something, that these vascular beds, where we induce lesions with compounds, are also vascular beds that are prone to spontaneous disease, and we need to do something to understand why.

To bring you up to speed with what we see to be the problem, I want to show you a few slides as to—so you can understand what the lesion looks like.

[Slide.]

This is a rat exposed to a dopamine

agonist, a mesenteric artery. Dopamine—Fenoldopam, in this case—induces a segmental medial hemorrhage and necrosis in the rat mesenteric arteries. This artery is about 400 microns in diameter. It's one of the main—secondary branches of the splenic artery. Ultra-structurally, you can see the—if you're looking down at the surface of the endothelium, in this case, and the honeycombed appearance off to the sides are areas where smooth muscle cells have disappeared—undergone necrosis and disappeared—and the voids are filled with red blood cells. You saw the hemorrhage in the previous slide. You can see the red blood cells in this picture. And look at the endothelium, which normally—

[Pause.]

Now you'll all see my fine tremor.

[Pause.]

How do you work it, Jim? Which button. Ah. Okay.

We talked about the red blood cells that have filled the voids in the smooth muscle that has disappeared. Also, look at the endothelium, which is important—and we'll come back to this later. But the endothelium is normally flat, pavemented,

it's pushed against the internal elastic lamina, because it's this pressure on top of it, and shear stress and hoop stress.

The endothelium in this animal is raised, it's swollen, it's separated one cell from another, and there are many white blood cells attached to the endothelium, and there are several endothelial cells that appear to be sloughing off into the circulation.

[Slide.]

This is another animal, also exposed to Fenoldopam. And you can see in this animal, the—this is an area where smooth muscle used to be, and it's now filled with almost 100 percent platelets, and a few red blood cells. I'm showing you these slides to sort of see some ideas as to the kinds of biomarkers that we would look for, given this kind of scenario.

The endothelium in this case, which is here, is—we haven't—there's not a lot of it in the picture, but it is necrotic and, essentially, not present.

If you look at an animal that has been allowed to recover from this lesion for three days, again exposed to Fenoldopam, you can see that the

smooth muscle is beginning to be replaced. There's still some hemorrhage cells that are sticking to the endothelium are neutrophils, primarily. They're migrating through, and there's adventitial inflammation, including mass cell degranulation—which was recently reported by Dr. Zhang at FDA.

So, again, that should give you some more ideas as to the potential kinds of soluble factors that we might look for in plasma.

I mentioned in my opening slides that these vascular beds are also beds where we see spontaneous disease. And if you look at 90 percent of retired SHR breeder rates, the vast majority of these animals will have a disease which is known as polyarteritis nodoza in the mesenteric bed.

If you look at an animal exposed to Fenoldopam for two years, you see a dramatic increase in the same kind of lesion. So, again, we have a drug-induced lesion that occurs in an area where we have spontaneous disease.

Many, but not all, of the compound-induced lesions in the rats occur in the mesenteric vasculature—not 100 percent, but a vast majority.

I want to move on now to some slides on

dogs—just a few more.

[Slide.]

This is a spontaneous disease in a dog in the coronary artery, known as idiopathic polyarteritis—also known as "Beagle pain syndrome." But this is a spontaneous disease, the cause is unknown. But it is a florid, inflammatory response, with lots of neutrophils, fibronoid necrosis of the medial smooth wall. The media is totally absent in this case. And this is a spontaneous disease—the dogs spontaneously recover. And there are lots of biomarkers that we know to look for in this disease syndrome.

Unfortunately, this occurs in the coronary arteries, and it occurs—yes, spontaneously, but it also occurs in toxicology studies. And, in many cases, more animals on a high dose will have this syndrome than in the low dose.

On the other hand, we have a wide variety of therapeutic agents that cause, morphologically, a very different lesion in the coronary artery and right atrial appendage of dogs. But in many times it's difficult to distinguish the spontaneous disease from clear drug-induced coronary artery lesions in the dog.

So, again, in the dog we have a vascular bed—namely, the extramural coronary arteries—that is frequently affected by a wide variety of pharmacological agents. And in the same vascular bed, we have a spontaneous disease.

So, once again, I there are some links here that we need to more clearly understand, through new technologies.

[Slide.]

Lastly, one slide from a human case of hypersensitivity angitis—and I hope, by now, you can see that what occurs in humans is morphologically very different than what we see in animals. And I think, if you look carefully, you can see some eosinophils in this lesion—which is the hallmark of hypersensitivity angitis in humans.

And this is a case—this is a skin biopsy from a patient who was taking an experimental drug, and the patient developed a rash, and this is what you see histologically. It's not that uncommon, but it doesn't happen in toxicology studies—in my experience.

So I want to talk, then, through a few cartoons about what the problem is.

Normally, we have blood flowing through

blood vessels—neutrophils very happily swimming along. And the neutrophils—the blood is under a variety of different biomechanical stresses. One is called "shear stress." Shear stress is a function of flow, divided by the cross-sectional area of the vessel. Shear stress is the force that tends to strip the endothelium off the internal elastic lamina as the blood flows by. And you can appreciate, based on the formula, that in order to control shear, the only one way the vessel can reduce shear, and that's by dilating or thoroughly relaxing. Because you can see that the diameter is indirectly proportional to flow—I'm sorry, shear.

However, if the vessel thoroughly relaxes, the vessel wall becomes very thin, and that does a very good job at controlling shear, but it does a very poor job of controlling tension. Because tension, or the forces that tend to explode the blood vessel wall, is a function of pressure and radius, but also indirectly related to wall thickness.

So if the vessel is controlling its shear by getting thinner, the hoop stress increases dramatically. And many of us believe that these biochemical events are very important in the

induction of lesions, and endothelial compromise.

So how does this work, then, in a cartoon? And I think if you remember the three-day recovery slide from Fenoldopam, you saw the neutrophils pavementing against the endothelium, there's endothelial compromise, red blood cells and platelets—and the platelets in this slide are the white oval things at the bottom—have migrated through the compromised endothelium, and that's all been influenced by a variety of potential biomarkers—the selectins, ICAMs, VCAMs, PECAMs and all the items I have listed at the bottom of the slide, then all become fair game for—as opportunity areas for biomarkers. And sufficient to say, if you are human, this similar kind of even would be happening, but resulting in a very different morphological picture—and, primarily, we would be looking at eosinophils in that case, which are depicted in this slide, and not neutrophils.

So then, in summary, we have identified in our document that you've studied, I'm sure, three potential mechanistic areas where we might look for potential biomarkers. And one is injury as a result of biomechanical change within the vascular lumen.

Second—which I have not discussed today in detail—direct pharmacological or chemical injury to the vascular endothelium—and we have many examples in this category as well.

And, lastly, immune-mediated vascular injury, or vascular compromise, which is classically seen more frequently in humans—but it is seen in animals with some of the biological agents.

So the Committee, then, intends to focus on identifying biomarkers that would be involved in these three major categories of drug-induced vascular injury.

So, in summary, regardless of mechanism, endothelial compromise appears to be an early and important—and an important event in vascular injury in rats and dogs. Drug-induced lesions in the rat and the dog appear in sites of spontaneous disease frequently, and this complicates the interpretation as to what this exactly means, I think, from the regulatory and safety perspective.

As stated early, in the beginning, common drug-induced injury in humans is not, or is rarely, observed in toxicology studies. Our animal models, then, you might conclude, are not that good at

predicting these events in human.

Common drug-induced vascular lesions in animals are not known to occur in humans, and have unknown relevance; not known to occur, once again, because we don't know how to measure. And that's the purpose of being here, is to figure out and identify potential biomarkers.

[Pause.]

I'd like to stop here, just briefly, and ask if there are any questions about the issue that we're here to resolve?

Lastly—and in the white paper—one of the Committee's charges was to confirm that this is an issue worth resolving. And let me say, in this slide, that I think it's from the EWG's perspective, I think this clearly is an issue that requires resolution, and we're prepared to move forward and to do that.

But let's just ask a few questions about the issue, so that we clearly understand it.

Joy?

DR. CAVAGNARO: Okay. Can you comment on other species—I guess, most, notably, non-human primates. But the information that you have from other species?

DR. KERNS: That's a good question. I haven't really focused on primates or mice in this presentation, because there isn't a lot known. But I can tell you that many of the compounds we deal with do cause lesions in primates and mice.

DR. CAVAGNARO: More similar to the dog and the rat, versus the humans.

DR. KERNS: That's correct.

DR. CAVAGNARO: So even when you suggest that there's no predictive model, that includes non-human primates.

DR. KERNS: That's correct. So that lesions in the species that we usually use—primates, dogs, rabbits, as well—what have I missed?—mice and rats--

DR. SISTARE: Pigs.

DR. KERNS: --pigs—yeah, right, pigs, Frank—the lesions that we see do not mimic what we see in humans.

But, nevertheless, we have to deal with it from a safety perspective and a regulatory perspective. We're trying to learn how to do that.

Any other questions about the nature of the issue?

DR. GREEN: Two questions, Bill. I didn't

see anywhere in the paper the stated clinical incidence of this lesion?

DR. KERNS: That's a good question. The—well, the lesion we see in animals—keep in mind--

DR. GREEN: The human.

DR. KERNS: The human lesion—yes. Hypersensitivity angitis, also known as leukocytoclastic angitis is a rare event. I don't have the actual numbers, Jim, but it is—can anybody help me?

DR. SISTARE: One study just recently done was looking at drugs approved, like, up to 1996. It was a member of my staff, Jim Weaver, actually did the study, and looked at all adverse events reported—I forget how far back it went—since the original data base. We've switched to a new data base in 1996. But up until that point, looked at all adverse events, and he was focusing on immune events. He counted things like rash, and he counted anaphylaxis, and he counted vasculitis. And when he looked at all those adverse events, and he tabulated—rash was the most common, the most common adverse event. But vasculitis actually counted for 6 percent of the immune-related adverse

events—the term "vasculitis" appeared.

Okay? Now, that's a very broad term, and it would cover all these other things—angitis and these kinds of things. But that is the immune-related—to be clear. I mean, what Bill is saying is that oftentimes the animal is not a good indicator of immune-related human events. So, you know, our animal models to predict hypersensitivity reactions in humans, there's a blind spot there. WE need to do a better job at that. We have guinea pig tests and things like that, which some people question how good they are. But vasculitis, the immune-related—again, accounts—I don't know what the overall incidence, but of immune-related events, it accounts for 6 percent.

But what Bill is talking about here now, in terms of the kinds of histopathological findings that are being seen in these preclinical studies, we don't know what the incidence of that might be in the clinic, if those same agents are given in a clinical setting, at certain doses. That's a—we can't answer that question, I think.

DR. KERNS: I mean, I can provide some anecdotal information. My experience in talking with medical pathologists over the years—people

have a lot of experience. You know, the kind of changes we see in animals, they don't recognize as being seen in humans in post mortem, from autopsy studies.

So it is—this is the conundrum.

So, Jim, I think the answer to the question is: it's not common, it's not rare, it's somewhere in the middle.

DR. GREEN: One other question: I take it that, particularly in the nonclinical studies, attention was drawn to those lesions in the dog and rodent because gross observations were seen initially.

DR. KERNS: Yes, these observations were initially recorded in dogs and rodents.

DR. GREEN: So—I mean, thinking about the sampling strategy that is employed in all of the toxicology studies, where a vessel—a small segment of a vessel is identified and taken, in the absence of any kind of directive, gross lesions to draw your attention to that, is there—has there been any discussion about the fact that maybe these lesions have been missed in a more subtle form just because they were there but we didn't see them? I mean, we're always subject to sampling that's done,

essentially, within these studies. And what is noted in the paper is some comment about different sensitivities in different anatomic regions.

So if you weren't drawn there, there could perhaps be more subtle lesions that are occurring at a very low level, and we're just—our incomplete sampling strategy missed them.

DR. KERNS: It's a very good point and, quite possibly, you're correct. I think one of the things that I think people in the PhRMA are tuned into now is that certain classes of drugs you would expect to see these kinds of events. And so there is focus on these vascular beds.

We're going to talk a little bit later about our standard model that we've put together in the rat, and we have addressed the sampling issue in the rat in that study.

DR. SELKIRK: In that same regard I was wondering if you can't—based on what you've seen in animals, and lack of what happens in humans and what the literature says, if you can differentiate that possibly in animals it's a more mechanical problem versus some sort of mediated hormonal or biochemical addition in human vasculitis?

DR. KERNS: Let me just clarify that. In

animals, one of three possible mechanisms of vascular injury is potentially biomechanical. You know, immune mediated is also a realistic probability and it happens. And direct drug-induced cytotoxicity does happen, as well.

DR. SELKIRK: But does there seem to be a mechanical component in the human problem, then? At this point?

DR. KERNS: In humans with hypersensitivity angitis it is probably a type-3 mediated response—immune mediated.

Do you agree with that, Frank?

DR. SISTARE: I think your answer that these are—there seem to be at least three mechanisms, and they're probably overlapping. Maybe some classes of compounds may dominate one mode of action versus another. I think it's really difficult to answer the question that if you have something which has a biomechanical effect, does that potentially contribute to—if you also activate immune components, so you activate cellular signaling which up-regulates adhesion molecules or something like that, and does some other things, would a biomechanical effect also contribute to that. It's possible. It's hard to answer that

question.

You know, there seems to be a growing attention to cardiovascular disease in humans, as long have been anchored in our diet, our cholesterol, our lipids, but there's growing attention to the fact that inflammatory mediators also seem to be growing—good prognostic indicators of vascular disease, and risk for heart attack, and stroke, and things like that.

So, it seems to be, again—I don't want to over speculate, but it could be that there's an underlying vascular inflammatory component to a lot of human cardiovascular disease that has been ignored for a long period of time. And I don't want to say that, you know, 90 percent of the drugs we're taking are causing problems. I don't think that's the case at all.

But this—I think, you know, the kind of questions we're asking here will bring attention to an element of something that we may have ignoring for a long period of time. And I think Jim's point—you know, the fact that a lot of these lesions are seen microscopically—you know, once you know where to look, and you start using the microscope, you start seeing things that you may

not have seen had you just looked at five or six different tissue sites, and a routine tox study, and not done—not been drawn there by some sort of macroscopic observation.

So, you know, I think this is an interesting set of experiments that need to be done, and bio-markers that can be identified which could prove fruitful in a clinic.

DR. CAVAGNARO: So, just to clarify—so the strategy is to try to be—to find more sensitive indicators of the current clinical situation, and not be more sensitive of the current lesions that you're observing in animals right now.

DR. KERNS: Just the reverse. I think the charge, as I understand it, is to first identify biomarkers that are robust in preclinical species, and then try to transition them into the clinic. So we can—primary objective being to prove one way or the other, do the changes we see in animals occur in humans?

DR. CAVAGNARO: Okay. So I'm right, because--

[Laughter.]

DR. KERNS: Okay. Maybe I didn't understand your question.

DR. CAVAGNARO: We don't really—I mean, what I understood is it's not predictive of what we're seeing in the humans. And it seems to me that if you understand the human pathology, and can understand biomarkers, the goal would be to try to capture those biomarkers more sensitive in the animals.

But to characterize—I guess I'm a little bit confused—to characterize the lesion being more sensitive, and characterize a lesion that's occurring in animals that's not predictive of humans seems, to me, a little—I guess I don't understand the logic.

DR. DOULL: I think, Joy, Frank is saying that the primary mechanism for the two things probably is the same. Therefore, one—the charge to the committee is to find preclinical biomarkers that are predictive. And the second charge is to find bridging markers—markers that work in preclinical situation that can also be used clinically.

So, you know, you could, in fact, accomplish the first charge and not the second one, which would be less useful.

DR. CAVAGNARO: But if your goal isn't to

find --- if your goal isn't to focus on the currently known human potential consistent with the human disease. I mean, you showed that cartoon there. That's where you're going to focus on—of that acute injury, those biomarkers—right?

DR. KERNS: In animals first.

DR. CAVAGNARO: No, no, I understand it's in animals. But the biomarkers are focusing on the human lesion versus the animal lesion.

DR. MacGREGOR: But one of the things that's not clearly known is whether those—just because you do see a particular kind of immune-mediated lesion in the human, that doesn't necessarily mean that if the animal effect carried over that the—that may be largely spontaneous in the human. I doesn't mean that would necessarily carry into the human model.

So one of the key questions we're hoping this group will address is the following.

We know that in animals this type of lesion that's seen in animals occurs frequently. And the question is how confident can we be that that does not occur in humans. And do we have appropriate biomarkers to be able to address that question—and I think we're all in agreement that we

do not have those currently. And then one of the questions for the group is there a potential for a biomarker that will allow us to address that question; that is, that what we see in animals in fact is not occurring in human.

DR. DOULL: If we don't do that we're just predicting for rats and dogs is all.

DR. KERNS: I mean, that's well stated, Jim, and that's my understanding of the charge.

DR. CAVAGNARO: Oh, okay. Well, then I'm—because I guess I was trying to see whether or not, as part of that, we were also going to try to—this incidence of 6 percent or whatever you're saying, try to—I guess that was—okay, so I'm at the other part of the equation--

DR. DOULL: I think so.

DR. CAVAGNARO: —and that is to try to be more predictive—to design the animals to be more predictive of what's actually happening in the clinic, which we're not doing that as well, either.

DR. SISTARE: So that the human vasculititities—I mean, that's a good question, too. But you're right—I mean, that isn't the primary focus. The primary focus is we're seeing this huge—we're seeing a very—an—we're seeing a

relatively common signal in a number of pharmacological classes of drugs which are coming to the agency for development, for approval for clinical trial capability, and there is consternation. We don't know what do to here. We can only go so high with a dose, then we start to see these lesions in animals. So you've got to stay below that dose.

But, it may be totally irrelevant, and we don't know. So we need a way forward. We need a scientifically grounded approach that will allow us to monitor what's happening here. Okay. So that's one approach.

Now, you bring up a very good question. Now—but I think our thinking is that as we learn more about all the different components that are involved in the generation of these biomarkers in these animal models, I think our thinking is that there will be a collection of these biomarkers that would be applicable to the human scenario, and that some of these manifestations that we're seeing in the human, there may be some biomarkers that arise that would be overlapping, even though the mechanism may not be exactly the same, there's going to be some overlap. So that it may be

helpful.

So, that's a hope. The problem is that these types of injuries that we're seeing in humans are so unpredictive, it's so difficult to do those kinds of studies, to systematically look at that, so the light is brighter on the animal sides, and we can systematically control all that, and we can make a faster speed, I there for Frank, I guess—from the chemical—since it's a generalized chemical phenomenon, meaning large amounts of drugs seem to do this in humans, has there been any attempt at just a straightforward structural activity relationship, to see if certain chemical structures have a predilection for this effect?

DR. SISTARE: In humans—again, it's different from animals. There is an SAR effort going on. I mentioned Jim Weaver—and Ed Matthews, and Joe Contreras' group—are doing an SAR analysis for all immune-mediated type events, and trying to develop a model that may capture it categorically, whether there is some sort of alert that indicates that kind of a thing. That's ongoing. That is ongoing.

But the other side of the coin, in terms of alerts that indicate what compounds are causing

these things in animals, and we don't know what's happening in humans, we're not going there yet. No.

DR. PAPOIAN: I'm Tom Papoian, Sanford drugs.

I just wanted to comment to the question Joy brought up about the bridging, or the commonality, or the differences between the lesions that we see in the animals and the predominant concern for humans, it's not necessarily the immune-mediated lesions, but atherosclerosis and ruptural plaques, which is attributed to an inflammatory reaction, which leads to heart attacks and stroke.

Wether those two phenomena are similar or different; whether the animal lesions or the effect of inflammation on animals has the applicability to humans, I think, without quoting the—some results from our previous expert work in group meeting, I'll say one of the active contributors presented some preliminary data to show that the drugs—one of the drugs that was tested on animals produced increases in a marker that is commonly associated with inflammatory reactions in humans.

So, there is a very good case correlation

there that the lesions that we do see in animals may have applicability to the human clinical situation.

I just wanted to make that comment.

DR. KERNS: Okay, thank you. I'd like to continue now.

Progress, to date, over the past two years: we have, through the committee, as I mentioned earlier—the committee is a collection of disparate skills and interests, many of which have nothing to do with vascular injury. And we spent a lot of time over the first year, just bringing everyone on the committee up to speed with the issues that we were trying to solve.

And that is behind us now, and we've addressed a lot of issues along the way, dealing with that, including terminology and lots of details and mundane things. But I think the committee is now 100 percent on board, with a clear understanding, as you are, of the issue.

We spend a considerable amount of time bringing together a standard protocol in the rat, that we have reviewed in its final form at SOT last year, and has now been agreed and published in our minutes.

This is the protocol, Jim, that addresses the sampling bias, in addition to a number of other things, and it will be the protocol that we will use to generate tissues to pass around to different investigators around the country.

We still require some more discussion, though, as to how to manage the data, and movement of samples around, and all these issues coming from these s, if you have a standard protocol, you must have standard compounds, so that we're all looking at disease induced by a standard set of compounds. Sounds simple, but to get the compounds we would really like to have, they're really not available to us, because they're proprietary and difficult—and you can always make somebody else's compound. But I think in this environment, that would not be the appropriate thing to do.

So we've identified three compounds that we think are available to us. One is Fenoldopam. One is a PD-IV inhibitor named CI-10-18, and one is dopamine. Why these three compounds? We had one agonist. CI-10-18 is a phosphodiasterase IV inhibitor. And dopamine, at high doses, is primarily aan alpha agonist.

The lesions induced by dopamine versus

Fenoldopam are morphologically different. I haven't gone into the detail today. And we—you might expect the biomarker profiles might be different—but we don't know.

So, we've chosen these three compounds because we believe they're accessible. Dopamine we can buy. And a lot of us at the committee level have a lot of experience already with these compounds. And certainly FDA does.

We are in the process of crafting a letter to the suppliers of Fenoldopam and CI-10-18, and that letter—we're going to come to that later, is something that I need some input on from the NCSS.

We have put together—and it's published in the White Paper—a list of--large list of potential biomarkers in the table, with references to support them. And, also, we have come to—put together a short list of biomarkers that we think have high probability that we can deal with today. And I'll tell you about that.

We've identified soluble E-selectin as a high priority potential marker, and we have a proposal on the table that is currently being reviewed to develop the reagents required to pursue this.

Another thing that you need to understand is that the—in the table in the report is a huge list of potential markers, but in order to do studies you need reagents. And rat reagents and dog reagents are not that readily available. So, to really do good work, we have to make the reagents, and that's the purpose of the E-selectin proposal. And it's just the beginning.

Joy?

DR. CAVAGNARO: So those three agents, there has been some incidence of—in humans, for all those three agents.

DR. KERNS: No, these are compounds that cause lesions in animals—not humans.

DR. CAVAGNARO: So there are no data—so, in your clinical data base that you're looking at, these agents don't show up.

DR. SISTARE: Not the hypersensitivity angitis. These don't show up in that category. You know, we're talking about a different type of lesion, and we don't know, in humans, whether these might cause those types of lesions.

But I will say, for example, though, that if you think about the dopamine category here—okay, so, phenylpropanolamine, I know that that's kind of

mired in debate, but that was a drug that was taken off the market because of stroke and things like that—in women that were taking it for weight control. There is some old data showing that—in the rat—one could reproduce a cerebrovascular injury event.

Is it the same thing? I don't know. You know, we don't have those kinds of markers to see if, you know, you could measure in the rat model. Would you see changes in biomarkers that you could then dose into women and start seeing biomarkers increase—some of which go on to develop strokes, most of which do not.

Again, I know phenylpropamine is a little debatable, whether it should have been taken off the market, were the signals real and all this kind of stuff. But, you know, it is enough of a—you can't ignore it. You know, you can't ignore some of these things.

The PD-IVs—I don't think there's a PD-IV on the market yet. Am I—there's not one on the market yet. There's a lot of them in development, a lot of them in clinical trials, and a lot of the dose escalation—the concern is that we're seeing vascular injury. And some of those PD-IVs, they

happen in monkey studies, not human primates. So, you know, it adds to the concern.

Fenoldopam is approved. It is approved for emergency use—short-term use. And that's a risk-benefit decision that went into the approval of that compound.

And, I think, in addition, dopamine, given at high doses and as an alpha agonist, does cause peripheral vascular disease in humans, and that's been reported and published. But, once again, it's morphologically a little bit different lesion. But, nevertheless, it should be an area where we can induce change and look for biomarkers.

DR. KERNS: Lastly, I'll try to allude to, as I go through the rest of the slides, the exciting things that are going on on the research side from member companies that are sitting around the table, and active contributors that are sitting around the table.

So, I've tried to summarize, in brief, the—some, but certainly not all, of the biomarkers listed in the White Paper. And into acute biomarkers, ones that might be more reflective of the inflammatory process that we talked about earlier. And lastly, how can we use the links to

address this issue and bring a whole other new set of data to the table that we haven't seen yet.

Acute markers—I alluded to the fact that there was some endothelial sloughing in the slides that I showed you. There is some published data now, I think, from FDA showing that apoptosis markers are increased. And so we intend to develop reagents to look at soluble fasligend and soluble CD-44.

We're looking at circulating endothelial cells, as well. Surprisingly, we all have a low level of circulating endothelial cells. But when you perturb the endothelium via a variety of different mechanisms, both with catheters or natural disease in humans, your circulating endothelial count increases dramatically.

The reports in the literature are a little bit confusing but, nevertheless, this is an area that we intend to pursue with vigor. And some of the companies around the table are already doing this and generating data, using our standard rat protocol.

Colleagues at FDA have done a great job of pointing out the value of acute phase proteins in addressing—as a biomarker of inflammation. And

certainly they are increased, particularly C-reactive protein that Tom was alluding to. They are increased in a variety of different vascular injury syndromes in the animal models. But we need more data, and we need to validate.

And, lastly, figuring out how to capitalize on using tissue from our studies, doing GNRAs, doing proteomics, and metabonomics on urine or plasma, of which many of us around the table are already doing, there's a lot of data that we review when we get together, and it's always exciting, but it's difficult to interpret at this point. And I think that's the problem.

So we need—I think the solution to that is a lot more data, and a lot more people participating in the program.

We have a short list—at least I think it's a short list of markers that we're tending—but this isn't immutable—but tending to focus on at this point. And that's urinary metabonomics, an initiative being taken forward right now by Pfizer. Don Robertson si a member of our group, and he's supporting that effort.

GSK is spending a lot of time—and others—looking at circulating endothelial cells.

Frank's group at FDA, through CREDA, with Boeheringer-Ingelheim, and perhaps others I'm not aware of, are looking at acute-phase proteins. And also other companies around the table are doing that as well.

We have a proposal—many of us are interested in soluble E-selectin as a potential marker. And we have—the group has identified an investigator at DelHause University in Canada who actually has the rat E-selectin cell line—has a cell line that produces E-selectin antibodies—rat E-selectin antibodies. And we're working with this investigator right now to put together a proposal to allow—that will allow him to generate an assay system so that we can look at soluble E-selectin the rat.

There's a proposal on the table, and we're right now looking for ways to fund it.

So now I have four or five slides, in closing, which I've entitled "Discussion Points." And I think, Dr. Doull, I'm looking for—the committee is looking for an exchange of information here, or exchange, comment—we're looking to hear what you folks think of what we're doing.

[Slide.]

The White Paper, you have a draft of. And please consider it as a working draft. It's by no means a polished document.

However, it is our intention—and we're looking for your comment—to publish this as a review, somewhere—in the next six to nine months. The timeline of the committee is not really established. But the document needs polish.

I'm looking for your comment on this initiative, and also I—the committee would like to learn about the formal process to get NCSS ratification—and confirmation.

I think—my opinion, that's just me speaking—I think it would be very important, as Ken said yesterday, to publish these papers, having agreement, or the blessing of the NCSS. But I don't know clearly how to do that, and I'm looking for guidance.

[Pause.]

That can come from anyone.

[Pause.]

Any comments?

[No response.]

DR. DOULL: Well, as we mentioned yesterday, with the cardiovascular one, there are

two issues. One is a scientific issue. And I think, clearly, the NCSS will give you feedback on our scientific interpretation of where you're going and so on.

Then there is the other problem, and that is the one that meets the FDA requirements. And I"m not sure we fully understand what those FDA requirements are, in order to publish it with the imprint of the NCSS on the publication.

DR. KERNS: On behalf of the committee, would it be possible to action some one, or some small group to help Ken and I understand the process more clearly? Jim, is that something that you could take on?

DR. MacGREGOR: Well, I mean, I think clearly the first step in the process is the discussion that's happening right now, and to get feedback form the subcommittee, and to determine if the subcommittee feels that the document that's been put forth is a valuable document, and is on the right track. And then, the next step would be, if that's the case, when this comes to a point that everybody's comfortable, that clear paths forward have been defined, then for the subcommittee to consider which of those might be followed. And if

there—and to come out with a recommendation to FDA that certain paths should be followed, and that support for those paths should be sought.

DR. DOULL: Let me back—follow-up on what Jim is saying.

We have talked off and on about publication as a scientific review and a peer review journal, and so on. And we've also talked about submitting that report simply to the subcommittee. I think it's going to be more valuable for what we want to accomplish if it's out there in the peer review literature. And so I think that's really what you're asking—is how do we go about putting a review paper out in the peer review literature which, in fact, has the cooperation, and collaboration and ratification, if you will, of the NCSS.

DR. KERNS: That's correct.

DR. DOULL: And that's what we'll explore.

DR. KERNS: Okay.

DR. DOULL: But before, actually, we do that, of course, we will need both from the cardiovascular paper—we've had the outline, now we'll need the White Paper which spells out, as you have done, Bill, all of these different things for

the committee to actually go through piece by piece and give you our comments on that.

DR. KERNS: Okay.

DR. DOULL: We may have to have a little time to do that, because there are several members of our subcommittee who aren't here, and I think they all ought to have an opportunity to review the paper, and we'll send you our conglomerated comments.

DR. KERNS: So, I'd like to suggest, then, that—and please comment, Frank and Tom and what others are here—that, you know, what we have given to you is a working draft. We would like to finalize that, then, over the next--month? That's a positive nod?

[Laughter.]

DR. KERNS: And send you a final—a penultimate draft for peer review, then, in October sometime.

DR. DOULL: That's fair enough. We gave you a challenge, now you can give us a challenge—time challenge, at least.

DR. KERNS: Okay. Good.

Sorry—Jim?

DR. GREEN: Just one comment first. I think

that in my review of this paper, I think it would be an excellent contribution to the literature, and a review, not only for this particular issue, but it can serve as a template for other issues that we're looking for biomarkers of either activity, efficacy or toxicity.

So, I think—I encourage the committee to proceed forthwith, and get something like this out into the literature.

One comment that I will have, though—and it gets back to my question about, you know, how big a problem is this issue? And I don't think it's well reflected in here. And I think, in order to—and, obviously, you're getting a lot of interest and support from major pharmaceutical companies who are committing their resources. So they believe that this is an issue that somebody—or a group within the FDA thinks it's an issue. So perhaps this is why they're paying attention to it. But it's not clear to an independent reviewer as to why—you know, what is triggering this.

Now, one of the things that I would also encourage you to think about, and perhaps reflect in here is—you know, why—what is the rationale for focusing essentially on the model that you're

choosing—the rodent model. And is it just history of experience? It's practical?

Well, you know, the situation that you're presented with right now is that there's a disconnect, essentially, between the presentation of the pathology in the human setting, and then what's reflected in both the dog and the rodent models.

So, some would perhaps say that either of those models don't reflect a—quote-unquote—"gold standard" to reflect the human pathology. So unless you're making a case in here as to why the rat, why the dog—I mean, perhaps it's just simple anatomy.

DR. KERNS: Right.

DR. GREEN: I mean, I would think—is the blood vessel anatomy and biochemical structure of a rodent most similar, essentially, to that in a human, normal or pathologic setting? Is the dog that way? Or is a primate that way? Or some other model.

It's not clear to me, essentially, what the rationale for that selection would be. And the context that I'd bring this up in is we develop drugs all the time in animals, and we're looking

for activity that is putatively thought to reflect activity in humans. So if we find a model that we believe—this, for example, clot-busting drug—essentially if it's active in dogs then it's likely to be active in humans. And why is that? Because the correlation has been set up, and then some would refer to perhaps that model as the gold standard.

So whatever comes out of this with respect to biomarkers, we're going to be in a situation of trying to—or at least somebody's going to look: what's the clinical relevance of this observation? So if you haven't made a good case, essentially, for why you've selected this model, there's somebody that's going to look at this and say, "Well, it's a different lesion."

That's the only comment I would offer.

DR. KERNS: I think all very good comments, and we'll certainly take those on board, I think, in the next iteration of the document. Particularly, I think, reviewing the incidence data—clinically—I think is an important point that we need to cover.

I think—let me just address your final comment, though, Jim—just to make it clear. And

this is my understanding of the charge.

And that is, we have a problem in animals. And I think what we're interested in doing is developing a set of biomarker profiling to demonstrate that these changes do not occur in humans. Okay? So I think, for me, that's the first objective.

And so in that sense, then, we're not really dealing with the human disease—okay? Because of leukocytoclastic angitis, there are markers in clinical—human clinical medicine that are elevated in hypersensitivity angitis. They're not good markers, but they are used.

We've looked at those markers in our animal models and we don't see increases—okay? So, once again, what we're doing is developing a set of markers that we can use in a phase I, eventually, we hope to demonstrate that the changes we see in animals do not occur in humans.

Sorry to keep reiterating that, but that's an important point.

DR. CAVAGN-invasive or non-terminal. I mean—so we can't focus on histopathology.

DR. KERNS: No. These are all non-invasive.

DR. CAVAGNARO: Right.

DR. DOULL: I agree. I think Joy and Jim have pointed out something that would enhance the document considerably. You know, there's the argument in tox that the rat gives us the wrong answer. In actual fact, when you look at most of those cases, the rat really isn't all that wrong. It's just that we don't understand while alpha-2 globulin is different, you know, in one species and not in another. Once you really understand that, then you understand it's not really an exception it's just an aberration in most of those cases. And that really is what we need to understand here.

That's why it's so research focused, rather than the presentation that we heard yesterday on the tropins.

DR. KERNS: Good points, Jim, and we'll take those on board in the next iteration of the document.

Joy?

DR. CAVAGNARO: So, in the survey of the lesion in—presumably the studies were done in both dogs and rats, classically. Is it a hundred percent of the time that both species get it? Do rats get it more predominantly than dogs, and

that's the rationale for the selection of the rat?

DR. KERNS: In my experience, some drugs cause lesions in multiple species, and some drugs cause lesions only in rats or dogs or monkeys.

DR. CAVAGNARO: Right. But this particular lesion.

DR. KERNS: But the lesions that we're talking about here are seen, at the right dose, in rats at 100 percent. Okay?

DR. DOULL: Those four biomarkers you were talking about—specific ones. The selectin and the--

DR. KERNS: Well, we don't have any data yet on the biomarkers, but the compounds, I think—Joy was alluding to the compounds, the model compounds we're going to use: Fenoldopam, dopamine and the PD-IV inhibitor cause lesions in 100 percent of rats at the right dose.

And it just so happens, in this case, the PD-IV compound also causes changes in the dog, and dopamine also causes changes in the dog—and humans.

Jim?

DR. MacGREGOR: I might just get back to the reports and ask if everybody's clear about the possibilities for reporting. Because I think the

group has really discussed how to publish this report in two different contexts. And I think it's important for the group to have some clear understanding how they're going to proceed.

Clearly the group has done a tremendous job of pulling together a lot of useful scientific information that I think we all have agreed warrants publication as a scientific review document.

But the reason the committee was formed was really to develop a background that could be the basis for recommendations of the subcommittee, with the concurrence of the parent advisory committee, might make to FDA as the paths that should be pursued.

So that opens the possibility of a slightly different type of report, which would be a formal committee report that incorporates the scientific background into recommendations for courses of action that might be pursued.

And I think either or both of those are possible, and they could be done in a variety of ways, depending on the desires of this group and the working group.

I think clearly the scientific basis for

the scientific review is there. The question is the degree to which the committee feels they want to use these conclusions as the basis of a formal report, and whether that should go public, or whether that should be an FDA document, with some recommendations about what's the most valuable path forward to address this problem.

DR. DOULL: I would remind the committee that, you know, the name of our committee is the "Nonclinical Studies Subcommittee." And that is the charge essentially. The bridging biomarkers is the second charge. We would hope that the biomarkers that are developed in nonclinical studies would, in fact, be could bridging markers. But that whole issue would have to be dealt with in the kind of paper you're talking about, Jim.

DR. MacGREGOR: Well, maybe that's something that would warrant a little bit of discussion right now. I guess, in my mind, just expressing my personal opinion, for a non-clinical marker to be truly useful, it needs to be a bridging biomarker. And you really cannot completely separate the non-clinical from the clinical. You need to be thinking about those characteristics in both the animal models and the

human that are going to make it useful in that way.

In a way, this is an excellent model choice for an effort like this, because I think this is a clear need, where there are some morphological and mechanistic differences in things that are, at least normally, seen in the two species, with a very clear need for bridging biomarkers that can help bridge those pieces of information, and understand whether what's happening in animals does or doesn't happen in the human, and whether it's manifest in a different way, or just not happening—all those questions are still somewhat murky because we don't have appropriate mechanistic biomarkers to answer the questions.

DR. DOULL: But if those three mechanisms that Bill talked about are, in fact, the primary mechanisms by which these effects occur in dogs and in rats, then those mechanisms are likely to be primary mechanisms for damage in people.

So that, you know, that forms the basis for providing a set of biomarkers which have potential to be bridging biomarkers, if we understand them more full. I read that in your document.

DR. KERNS: I mean—both very good parts. But I think, from the committee's perspective, yes, it's a nonclinical studies subcommittee, but we are incredibly influenced by the fact that these need to be bridging biomarkers. So we can't ignore that as we move forward.

DR. DOULL: Well, when we circulate the document to the other members of the subcommittee, I think we need to talk about those issues, Jim, that, you know, we're thinking about a scientific review which includes all the information and so on, and also what we might present to, say the Advisory Committee on Pharmaceutical Science—as a recommendation.

DR. CAVAGNARO: So—for the clinicians in the audience—no clinicians? So, I was just wondering, in terms of the data, with tconcerned about, so that when we bring them forward to the clinic, we won't be able to distinguish--

DR. KERNS: Right.

DR. CAVAGNARO: —because they're elevated in a basal--

DR. KERNS: Good question. There are many clinical diseases where circulating endothelial cells—E-selectin and acute-phase proteins--clinical

vascular diseases are elevated. And that's all been published. And that is—in part, that influences our decision to look at these markers in animals.

But please keep in mind that our primary objective—if you remember the mandate on page two of your paper—it says, "To look for biomarkers that we can transition into Phase I." It says "Phase I/II," actually.

So I would envision, you know, in the first instance, we're looking at normal volunteers with a baseline level of circulating endothelial cells, E-selectin, is non-detectible or at baseline—whatever it is. So in that clinical experiment, then, we're going to be looking—and we should be able to see, in theory—clear increases in their changes.

So—as we get into patients with lots of diseases—vascular diseases, diabetes, atherosclerosis, smoking—I think it would be very difficult to find biomarkers that have specificity and sensitivity. And I think that's why we need to focus, at least initially, on phase I volunteers.

Anybody else have an additional comment on that point?

Was there another question here? Yes.

DR. ANDERSON: Do you know what they're looking for in the urinary NMR and, two, do you know whether or not they compare the animal NMR—I think you said plasma—to human the NMR of the human plasma.

DR. KERNS: Right. It's a good question.

At this time, the urinary NMR has primarily been focused on rat urine from rats receiving the Pfizer PD-IV inhibitor, as well as a couple of other compounds—but only in the rat. And I can tell you that there are clear pattern differences in the NMR spectra from rat's urine receiving these compounds.

To my knowledge, you know, this has not been transitioned into humans—to my knowledge. But that is something that we would plan to do eventually, you know, in the bridging stage.

DR. ANDERSON: Well, their probably looking at metabolites, I would guess. So that's why they were different than--

DR. KERNS: Yeah.

DR. ANDERSON: —those that don't have it.

DR. KERNS: I'm not a metabonomics person, but I think—you know, the—yes, there are

metabolites in urine, but also lots of fatty acids, many other compounds that are being looked at in the metabonomics profiling.

You know, metabolites clearly differ across species, and that could be--

DR. ANDERSON: I'm not a metabolite person, either. I'm thinking about what NMR does, and looking at--well, it might be interesting to look at the human NMR, as well.

DR. KERNS: The--

DR. ANDERSON: The human urinary NMR.

DR. KERNS: Right. But we're not--we agree, eventually that will--

DR. ANDERSON: Differences or sameness could suggest a lot of thing.

DR. KERNS: Right.

Frank?

DR. SISTARE: Some of the beauty of this effort is while there's some common protocols and sharing of data, many of the people that are working in this area are also doing things--you know, as Bill mentioned, we have CREDAs with other people, we have transfer agreements with other people, and there are other people that are doing--that are contributing to, like, the formation

of the document that are doing some investigations on their own—maybe with proprietary compounds, these kinds of things.

So, some of the investigators that are involved here, we've been working with—we generate samples, and we would share them with a collaborator who would do urinary metabonomics, for example, on some animals that we have dosed. And we're looking at, say, protein biomarkers in the serum. We'll have the urine, we'll send it to them, and they will do some of these analyses.

Now, I do know that some of the people that are involved here are looking at human urine as well; looking at cohorts of normals, and the human vasculitities—the clinical vasculitities, the Shirk Strauss, the Takiasu's, these kinds of diseases. And they are seeing differences. So it's encouraging.

It is a challenge—I mean, to see—you know, do like a principal component analysis, and look at patterns of these—they're intermediary metabolites of carbohydrate metabolism and protein metabolism, and fat metabolism that they're seeing in the urine. And when—it is a challenge to identify which of these may be the critical ones that end up

being the discriminatory biomarkers that you can hang your hat on. And there are certain controls. You have to watch diet—control diet, and make sure of these things.

But some of these things are being done. There's a lot of success. Jeremy Nicholson's group, for example, has really lon of vasculitis at Pfizer. And at Pfizer they are looking at human applications, as well.

DR. ANDERSON: I know that metabonomics has made a lot of progress in the last 30 years, but 30 years at Chicago they were tagging compounds with fluorine. And at that time I was the fluorine in spectroscopies, and I was running the samples for the people in the cancer research center. And then there's a big difference in what they do now. But that's why I was wondering about if there's a comparison between the animals and the humans, because that could perhaps tell a lot about what's going on.

DR. CASCIANO: I'd just like to make a comment, to follow up on that.

There are studies being proposed that would link metabonomics to the other omic technologies which would then help understand that

the portobations that are occurring in discovering specific intermediary metabolites by also understanding pathway changes that might be linked to them.

So those are beginning to occur in specific cases in rodents, so that hopefully that metabonomic data developed in the human would be more definable and credible.

DR. CAVAGNARO: So, can I understand—so the protocol, the proposed protocol—the rat protocol, then for that protocol—do you have the list of the end points? Right.

Okay, so for the protocol with the three—so each of the three drugs will have all of these markers? Or will they be selective? So for each of the three, will have urinary NMR, circulating—so that's the idea of the protocol.

DR. KERNS: The answer's yes—but minimally. Because we have—as Frank pointed out, we have a standard protocol, but there is lots of independent work going on within companies around the table. So, in addition to these and others, there will be many biomarker data sets coming to the table.

[Comment off mic.]

DR. KERNS: Yes. There's some technical

challenges. Doing the urinary NMR primarily has to be done at one site. It's difficult to do that and send the urine around. So this—I've got some negotiating to do. If Don Robertson and Pfizer's going to do all this work, I think I'm going to have to talk to Jack. So—but, in essence, yes.

I mean, we would hope to have a robust set of data, of not just these four but many different biomarkers including these, from at least these three compounds in the rat. And then, hopefully, we'd be in a position, as you'll see later on, in about a year, to make some decisions.

Moving on with points for discussion, I was very happy yesterday with the discussion about potentially moving under the umbrella of NCTR. And opens a lot of opportunity for us within the committee to not only get work done, but to collaborate with other scientists in an independent but collaborative way.

I think, with the—and I just learned yesterday about—and when I visited NCTR a month ago—about the new initiatives there in genomics, proteomics, metabonomics—Dan just mentioned.

I think in addition to those—that resource, in addition to the resource we haveully,

to expand our data base and knowledge.

And we believe—many of us believe—that there's great opportunity. You know, we focused on the logical biomarkers. That's the table in the report. These are the logical biomarkers based on what we think we know about pathogenesis. But we have no idea what's going on at the gene level and the protein level. And there certainly is a lot of information there that we need to generate, bring to the table, and influence decision-making.

And that remains to be done. Some of it—some member companies have already been moving in this direction, but the data are evolving.

So I see this as an opportunity. I hope you do, as well. And, you know, I think what remains for me as a committee chair is to understand the process as to how we get in the queue, so to speak, to access resources at NCTR—not something we need to talk about today, but it's information I think, as committee chair, I'd like to receive back from NCSS and NCTR.

I mentioned earlier that we have a letter—it's just a one-page letter that's being crafted, to send to the key stakeholders at Abbot, who owns Fenoldopam, and Pfizer, who owns CI-10-18,

two of the model compounds we intend to use.

We would like to access, say, a half to one kilogram of each one of these compounds. I have already received informal agreement that this is possible, but we need to send a letter to the key stakeholders—Jack is one of them, Reid Patterson and his colleagues at Abbot are the others—a letter from the NCSS, FDA, requesting the compound. And I need your comment or discussion on that topic, and agreement to move forward.

The second thing I need to know is that that is the easy part. Having receiving the compound—whatever we can get—how do we manage it—it's distribution to the customers on the outside? Is that something that we want to do through FDA? Or is it something we want to try to do through, in this case, Pfizer and Abbot?

In an informal discussion I had with Jack yesterday, his suggestion was—give it to FDA. Probably simpler than having Pfizer receive a hundred requests for material transfer. And perhaps that's the smart thing to do, but I don't know if we have the infrastructure here to support that.

So I'm looking for some discussion around

this topic.

Joy?

DR. CAVAGNARO: Let me understand. The Abbot Drug, and it's an approved drug, and is a marketed drug?

DR. KERNS: That's correct.

DR. CAVAGNARO: But the Pfizer drug is an investigational drug?

DR. KERNS: That's correct.

DR. CAVAGNARO: So that right there, that's a huge distinction, in terms of, I think, understanding—I mean, one's an approved drug and the investigational drug. And so now the investigational drug that—so I'm understanding that the data from these studies will all be public, obviously, because of the relationship, in terms of--

DR. KERNS: We have agreed within our committee that everything we do will be published--

DR. CAVAGNARO: Right.

DR. KERNS: —and public.

DR. CAVAGNARO: So now you're shipping investigational drug versus—well, I guess that doesn't make any difference in terms of animal studies.

DR. KERNS: It's not an investigational drug. It is CI-10-18 is a drug that has been looked out at Pfizer and terminated.

DR. CAVAGNARO: Oh, it's terminated.

DR. KERNS: Okay. But they are developing, as are many other companies, other PD-IV inhibitors.

DR. CAVAGNARO: Oh, okay. Okay. All right.

DR. KERNS: So the PD-IV inhibitors are being developed. They're in Phase III. And I'm sure, shortly, one or two of them will be submitted.

DR. CAVAGNARO: So the drug that they've discontinued, is that on stability? And is it being characterized? So, obviously, the approved drug will have its qualifications and, you know—so this drug, now that has been terminated, is it still being--

DR. KERNS: Tracked--

DR. CAVAGNARO: —tracked, in terms of stability--

DR. KERNS: Yes. Sure.

DR. CAVAGNARO: —and etcetera?

DR. KERNS: Yeah. That shouldn't be an

issue.

Dopamine, on the other hand, each investigator can buy from Sigma. That really is not an issue.

So it's these two compounds that, to really kick off our experimental programs—you know, we need access to drug. And my—the committee's recommendation is to try to see if we can receive a gift from these two companies.

DR. DOULL: The mandate of this subcommittee is to help our working groups in any way we can. So I think what we're saying is, we need to find out exactly how best we can facilitate what it is you want to do, Bill.

DR. KERNS: Okay. Well, our request then is to agree with the strategy to pursue this, if you think it's a good idea, via this introductory letter, in this case, to Jack Reynolds and Reid Patterson.

DR. MacGREGOR: I think this topic clearly moves to the mandate of the subcommittee, in terms of—as you said—recommending to FDA paths forward and mechanisms for taking these steps. So I think if a letter is to go out asking that materials be made available, I think in order to do that, the

subcommittee needs to endorse the recommended, or the identified approach—approach that's been identified by the expert working group. And I think, in my mind, the letter should probably go from the subcommittee, asking that they endorse the concept that these materials be made available for study under a common protocol that would be useful to FDA and its collaborators.

DR. DOULL: Yes, and I think we're at that point. The working group has made the request, and I think we need to explore our ability to, you know, facilitate that request. And we'll do that.

DR. KERNS: So, with your permission, then, we will draft a letter for signature by at least yourself, Dr. Doull, and maybe me and Jim. I don't know who the others are. But I think, minimally, yourself, from ht. So, in that letter, are we going to try to work through the other pieces? Because, one, you need to know a mountain, and how are you going to manage that.

DR. KERNS: Yes.

DR. CAVAGNARO: So the expectation is that that should probably also be part of the letter, as well, and not just--

DR. KERNS: Yeah—the detail will be in the

letter.

DR. CAVAGNARO: Yes, I think we probably need to provide some detail.

DR. KERNS: As to how it will be managed. Yeah.

DR. CAVAGNARO: Right.

DR. KERNS: I think, ideally, for the companies, it's one MTA coming to FDA. But I need to talk to Frank, and others here, as to how that could be managed. Maybe it could be managed at NCTR, as a distribution site--also is a possible way to do it.

Frank, do you have any thoughts?

DR. SISTARE: Yeah. Traditionally, whenever we obtain a compound from the regulated industry, it is through a legal document; through a material transfer agreement. And the standard format indicates that we cannot give that to anyone else. It has to—you know, when we're done with the study, we have to give it back to them or destroy it.

DR. KERNS: Really?

DR. SISTARE: So, the way it's written right now, that's the standard. That doesn't mean that it can't be amended. So that's something that

would need to be explored. And with the permission of the supplier, I'm sure, you know, we could come to some agreement. It just has to—we just have to make sure that, you know, there's no perception of any impropriety and all that kind of stuff.

DR. MacGREGOR: Yes, I think—I mean, I think clearly you'd need a material transfer agreement to do this. But I believe those agreements certainly can be structured to make material available for research purposes. I think another question is if the material is to be made available and distributed by FDA, then how are priorities set for how that would be distributed? I mean, I think that's something that needs to be done through the oversight of the subcommittee, really working with the expert group. I mean, that's the mandate that we gave to the subcommittee, was to identify paths forward to solve certain problems to advance the science, and to provide oversight of collaborations that could be formed to pursue those objectives.

DR. KERNS: That's a good point, Jim. So I think all that needs to come out in this --

DR. DOULL: Where we're at—we've received your request, and we'll do our best to find out how

we can help.

DR. KERNS: Okay. Very good.

Second, I think it's time for us to begin to think about planning for some sort of symposium in a year's time. It could be independent. It could be linked with cardio-tox group. It could be linked with ILSI, it could be linked with ACT, SOT—any one of a number of organizations.

But I think between now and 12 months from now, the contributing scientists around the table will have generated a lot of data. And I think we need to begin to plan the presentation of those data, and get other people around the table—more ideas, and so on.

So I think our recommendation is that—you know, I think Ken and I really haven't had time to talk about this, but how do we move forward along these lines, and, I guess, looking for discussion—what are your ideas. What are you thinking—with regard to the current state of the project? And how is it best organized? Is it independent, or is it aligned with some other meeting?

DR. CAVAGNARO: So, is the expectation—if drug is available, that some of these studies—that

there will be data to—so the October symposium of next year is to discuss the concept. Is it to --

DR. KERNS: There will be --

DR. CAVAGNARO: —will there be data available from these --

DR. KERNS: -- data.

DR. CAVAGNARO: —okay. So they'll be from this rat protocol --

DR. KERNS: Right.

DR. CAVAGNARO: —and now it will be an opportunity to present that at a more--

DR. KERNS: That's my whole—right.

DR. CAVAGNARO: Oh, okay.

DR. KERNS: Not just the rat protocol. Keep in mind there's lots of independent work going on around --

DR. CAVAGNARO: Right.

DR. KERNS: —the periphery, within companies, that is currently not available to our committee—formally. And I would hope that in the next 12 months a lot of that information could come to the table and be presented, as well.

DR. CAVAGNARO: Is it my understanding that this initiative won't be picked up by ILSI or other organizations; that we're not duplicating

anything—that this is given the go ahead that, you know, if we so bless this activity, that there won't be—or, if there are, it's more—not so much competition, but they'll look at another piece of it. So, in the end, we have really a collective data base?

DR. KERNS: That's a fair question. I think—my understanding currently, this is an FDA project. And ILSI is not involved. But I know Jim is—sits on the biomarker group in ILSI. Maybe he might have a comment?

DR. MacGREGOR: Well, I think, actually, this enters into yet another topic that we really haven't addressed, which is: having identified paths that should be pursued, you know, then where would the resources come from to do that.

Now, we've already heard that spontaneously, some of the people who've been involved around the table have already begun to do some things along the lines of the discussion—and that's terrific. And I think once courses are defined, we need to think about—and in my mind, ILSI would be one of the organizations that I might think about, that might be interested in certain biomarker initiatives that would come out of here.

And both at this group in its early stages, as well as some of the ILSI discussions, there's been discussion of trying to coordinate between FDA and ILSI priorities, to move forward in this way.

So I would think that at some stage we would want to make initiatives that come out of this group known to groups like ILSI, and other groups, who may wish to participate or collaborate, or to bring it int

I think we need to give some thought to what kind of a conference we're talking about; whether it will be a small conference, dealing with biomarkers for vascular injury, a broader conference dealing with biomarkers in general, or a big biomarker-type effort. And that would depend somewhat on whether it's ILSI, or SOT.

The ACT thing that Ken did was very valuable to that committee, and it was very focused. And, you know, that has some merit in that it gets a lot of feed back to your working group.

I guess what I'm thinking is that we also need to explore that, Jim. That has to do with the future activities, really, of NCSS—you know, how we begin to put those together to publicize all that

kind of activity, and how we begin to plan the future things that NCSS will do. We're not going to be limiting only to cardio and vascular-type biomarkers. Eventually we'll broaden that.

DR. KERNS: Well, it sounds like there's reasonable consensus that this is something we should pursue in some format -- and in 12 months' time. And I think the committees, and maybe Ken and I and Jim, need to take that on Board and come up with some plans and strategies to send back.

DR. MacGREGOR: I think we need to not necessarily at this moment—but we need to set a time-line for the NCSS formal review of these proposals, and then to get some clear feedback from the subcommittee, their endorsement of these payouts. And then structure that into the next meeting of the subcommittee to determine where things should move.

DR. KERNS: Just for information, when is the next meeting?

DR. DOULL: We haven't actually decided. This meeting—you know, we're a little unstable, because we weren't sure exactly where NCSS really was—at home, or functioning and so on. I think now, then, although all the details of that have

not been resolved, the intent is clear—Dan's intent and Helen's intent.

So I think—the subcommittee now feels fairly comfortable about all that, and I think we are now in a better position to move ahead and make some plans for the future.

DR. KERNS: Let's move on.

The next item relates to the biomarkers. You know, we have provided to you in the table, in the report, a long list of potential markers, based on probable pathogenesis.

My question, I think, from the committee is what do you think? Do you have some other ideas—other things that we should be thinking about at this point in time? We've also tried to identify what we think is the low-handing fruit, so to speak, on this slide. And, you know—what are your thoughts, comments? Do you have other ideas, or should we be moving in other directions?

That was a question to the committee?

DR. DOULL: It's an overwhelming list.

DR. KERNS: Any ideas?

[Pause.]

Ken? It's just a comment, and I'm sure that your working group has already discussed this,

and that is being able to distinguish between a primary and a secondary adverse vascular event. And that some of the markers that you have listed up there would probably change in response to a secondary toxicity, as well as a primary.

I think it's just the nature of the beast that you're looking at that there's not real clear primary specificity.

DR. KERNS: Very good point. And, I think, you know, specificity, sensitivity are issues that we will have to deal with down the road. And I think, at this—what you see is a shotgun listing at this point in time.

I think the ones—the short list that I pointed out, are ones that perhaps have more specificity and sensitivity in normal animals and normal volunteers. But there's a lot more homework to be done there—but, ver good point.

Joy?

DR. CAVAGNARO: And is the protocol such that you will have multiple readings of those individual markers, or is it a single end-point?

DR. KERNS: When you say "multiple," what do you mean?

DR. CAVAGNARO: I'm sorry—over time.

DR. KERNS: Over time—yes.

DR. CAVAGNARO: Right. So the protocol is—and that's—what—can you describe just an outline --

DR. KERNS: Briefly, the protocol—these will be single—the model that we've set up are single-dose studies, subcutaneous exposure, high doses; animals are sacrificed at various times. I forget the details now—number of times—but maybe seven or eight time points over a period of about 48 hours, roughly. I can't remember the details.

And we'd be looking at a variety of different endpoints at each one of those time points, varying from, you know, PK to potential biomarkers, a routine clin path, histology, addressing the sampling issue that Jim pointed out.

So, a single-dose study. And so—so you have data to suggest that a single dose—you've seen these lesions at a single dose, obviously.

DR. KERNS: sure. These lesions occur within hours. The lesions I showed you this morning, early on—earliest events, endothelial compromise can be seen ultra-structurally within hours.

DR. DOULL: okay. Your committee—working

group has developed that protocol, and it's not in here, but we probably --

DR. KERNS: We should put that in there.

DR. DOULL: Yeah.

DR. KERNS: Actually, that was my intent --

DR. DOULL: —you could --

DR. KERNS: —actually, I forgot to do that, yeah.

DR. DOULL: Yeah.

DR. KERNS: It's a good point. We'll put that in the next draft.

That's a very important point. I didn't—and I forgot to mention that. But, in terms of time course, these lesions occur—can be initiated very rapidly. And that's why I think biomechanical is a high probability mechanistic path, I think—for some of the compounds, but certainly not all of them.

DR. DOULL: And I would add --

DR. KERNS: And, you know, regarding the model data, this—a lot of this has been published by people around our table. So we're all quite familiar with the details. And the single dose—the study paradigm is—should be no problem.

DR. SISTARE: I'm sure I would add that

we're sort of starting there, because that would be one of the easier ones to tackle—to be able to develop some consensus, in terms of being able to pick a lesions that you can pick up within 24 hours, for example.

There are other examples of compounds within the same class at lower doses that make take weeks or months to develop in some of the nonclinical studies.

And that's probably going to be more like the clinical scenario, where we won't go with such high doses. We'll go with a lower dose, and then it's going to—it may surface at some late time. So we have to be cognizant to those kinds of things, and sampling times, and—you know, markers that may go up and down real quick. Other markers that may go up and stay up for a length of time.

So, a lot of these markers have certain virtues, in terms of those kinds of kinetics. So that's why we had to take the shotgun approach to begin with.

DR. KERNS: Just for clarity, although we've talked about our standard rat mode, we'll put the protocol in the next iteration of the document. But there are several companies around the table

who are still looking at other species, which is important, as well. I know Calvert, sitting behind you, they're looking at dogs still, and that's very important.

But, on the practical side, Jim, we chose the rat for strictly practical reasons. And compound supply issues.

DR. CAVAGNARO: So, when we look at the dog, will we also be looking at the same endpoints, at least? Those core—so, you're defining a core set, you know, of minimal endpoints that will track with most protocols. Because if—we're not going to be ab--

DR. KERNS: Yeah.

DR. CAVAGNARO: —you know, if we're looking at too many different things. And so, for the dog initiative, then, is it clear that we're going to look at the same endpoints?

DR. KERNS: Right. At this point in time, the EWG does not have a dog initiative. There are companies that are going to continue to work in the dog, and as the reagents become available for the dog—yes, we'll try to look at E-selectin across species.

The problem, once again, is reagent

availability. So we're—and we're constantly looking and trying to address all those kinds of issues.

DR. CAVAGNARO: But you can at least take samples --

DR. KERNS: Sure.

DR. CAVAGNARO: —when you can, and store them, and for future. It just seems a missed opportunity if somehow—I know it isn't our initiative, but if it's going to add to our initiative, presumably, at some point, that at least whoever else is doing it will be aware, and be able to --

DR. KERNS: Save tissue.

DR. CAVAGNARO: Right.

DR. KERNS: Yeah. That's a very good point. And I—although we haven't specifically addressed that with the dog folks, or the monkey folks, I'm sure it's happening.

Can assume that Calvert—?

AUDIENCE: Yes.

DR. KERNS: Thank you.

Ken?

DR. WALLACE: Just a comment on the design. You've picked a few compounds where you expect to

see an adverse event, and you've done a very good job at formulating the path in which you should be able to detect those.

But I'm concerned about the possibility of seeing false positives. And have you considered including compounds that you could also assess the potential record of false positives, where you don't have a primary vascular injury?

DR. KERNS: That's a very good point. And we've talked about it within the group. And I think it's certainly something that we must do when we get to the validation stage—okay? But I think to keep the workload manageable at this point, we've chosen not to go down that path right away. But it's certainly something that needs to be done before we close out this project—to look at specificity. We agree.

DR. DOULL: One thing that our committee has talked about—subcommittee has talked about in previous things is this—what Joy mentioned, the data banking. You know, storage of samples and so on. There need to be facilities in order to do that sort of thing, and hopefully, that's some area—another area that we could perhaps facilitate in some way—as well as the agents that you use, the

samples that are collected—or both programs, Ken.

DR. KERNS: Additional comments on this slide—or questions?

I'd like to tell you a little bit—there's two last slides—our timelines, the EWG timelines, that were established in November of '01, which was this committee had it's first meeting in May of '01. November of '01 we established this timeline. And I'm only showing this to you to show you how hard the committee has worked to stick to the timeline.

And I think if you look at the items that we would set—we would do and accomplish, according to the timeline, you'll see—and I'm sure everybody will have copies of the slides later, that we're pretty much on target with meeting our objectives of coming to SOT in March of next year, having initiated —past tense—a lot of standard studies, begun to generate lots of information and data that we can review at a face-to-face meeting in March of next year.

The only thing that I think remains to be done is to develop a mechanism as to how we can begin to organize and manage all this information. And that's something the committee needs to take on

board.

We've talked about the symposium today, and I think that's something that is—I don't know the exact timeline, but it's an important piece to this that needs to happen. And it's on target.

And we're committed to working with the member companies, and the NCSS, to bring forward in November of next year some potential biomarkers for further investigation, supported by real data.

DR. CAVAGNARO: Well, I'll have to echo with Jim. I mean, this is an amazing effort, to coordinate as many folks as you have, in terms of—and their contributions. I mean, again, it shows that the concept is actually—you know, hopefully, may work, and hopefully we'll be able to support, you know, the concerns that you have and so -- to support, so that you'll meet those—the future, the future timelines as well.

But, I guess I was a skeptic, in terms of this whole initiative, I'll have to admit, back, in terms of vasculitis as being a huge—huge area, of great unknown. And I think you all have done a great job in terms of at least putting it into some, I think, context that I think that we actually can design studies. So thanks.

DR. KERNS: Well, thanks, Joy. And thanks from the committee. We appreciate it.

DR. DOULL: I talked to Marion Erlich about the program for the SOT for the Utah—it is, of course, locked up, so that any kind of workshop or whatever would have to be ancillary to that meeting.

That's not true for the ILSI meeting—for some of their meetings. But I think—that's one of the problems we'll have in our planning, is that those things do get pretty much locked up early on. So we need to think far enough ahead so we can really do that planning.

DR. KERNS: Right. And that's why I'm talking about October '03 today.

DR. DOULL: Right.

DR. KERNS: I think we're not ready in March for the SOT—we're not ready at that time.

I believe that's the conclusion of my slides.

DR. DOULL: Well, for the subcommittee, I'd like to echo what Joy says. We are really impressed. You guys have done a fantastic job. Both of our working groups have just, I think, far surpassed anything that we would have anticipated.

And it's—that's the important part of what's going on, is the momentum. Both committees now have developed a momentum which is crucial to the future success of the program. And we're committed to maintain that.

Are there any questions for either of our working groups?

[No response.]

Well, I guess, then we'll go ahead and break.

Let's see. We're scheduled to come back at 10:15? Why don't we go ahead and do that.

[

Open Public Hearing

DR. DOULL: Kathleen is out getting an agenda for the Advisory Pharmaceuticals meeting, which is October. And we will present a summary of where our working groups are in that October meeting—Dr. MacGregor and I.

And so in order to do that we will need to get the couple committee members that aren't here, we'll need to get some feedback from them before we do that.

At this point, I think, officially, we are asking if there is any public comment. We have no

formal requests for public comment, but if there is any public comment we would welcome it.

[No response.]

Okay, I guess the minutes can show, Kathleen, that there was no public comment.

MS. REEDY: All right.

DR. DOULL: And we can move on.

MS. REEDY: Yes.

DR. DOULL: Okay.

Subcommittee Discussion

DR. DOULL: Well, at this point, we're scheduled to talk about subcommittee discussion, and the next steps. We've done that partially in the meeting that we had yesterday, and partly in the meeting, again, that we've had today.

And as I indicated previously, one of the concerns that the subcommittee has had in dealing with our working groups is that we haven't exactly known where the NCSS subcommittee, in fact, is going to end up.

As you heard from Helen Winkle yesterday, they are planning to do some reorganization within the Advisory Committee for Pharmaceutical Sciences. And at the present time it's not exactly clear what that reorganization—how that will look when it's

done. But I think we heard from Helen yesterday, clearly, a commitment to preserve the ability of the NCSS to make recommendations to the Advisory Committee for Pharmaceutical Sciences that would come for from our working groups. And we certainly will intend to do that.

And we also heard yesterday from Dan about the anticipated support from NCTR. So we're looking for that arrangement. We think it will really be exciting.

Well, I think, then, the question is, in terms of the working groups. And I - Ken, when we did—yesterday, when we talked about things that your working group was bringing to the subcommittee, you really brought us three issues that you wanted us specifically to deal with. First, you have an outline for the paper which you're going to put together, and you want approval of the subcommittee for that outline. I think yesterday we said that we did approve that. We thought that was an excellent outline. And I guess the minutes should show that the subcommittee encourages the working group to go ahead and put together that—the final draft of that.

Now the second issue that had to do with

that outline was the next step. If you identify the data gaps in there, which we're assuming that is part of that outline, then the question is the plans to fill those data gaps, and whether that should be part of the outline.

I think, as I recall from what we said yesterday, that was out intention—that you would, in fact, put together some kind of proposal which would fill the specific data gaps that you were talking about. And that the subcommittee, then, would look at those proposed plans and try to develop a procedure whereby we could help you achieve those plans to fill the data gaps.

I think how the subcommittee responds specifically to those recommendations depends somewhat on the kind of recommendations that you bring us. But our intent, you know, was to be supportive, to accomplish the goals of the subcommittee.

And the third thing we talked about is the cardiac group has focused, of course, on troponin, because that's a prime candidate. And the issue was: well, how about all the other biomarkers, you know. That certainly is a down-the-road agenda, and the question that you asked us was: how much of

that should be in the present document? And, I guess, my own feeling is we would leave that somewhat to you all. Clearly, you're going to have to indicate in there that the committee, in their judgment, looked at all the potential biomarkers and decided that the troponins were, in fact, the ones that they wanted to focus on initially, and have done.

The question then is, you know, whether there should be any review of other potential biomarkers to indicate the basis for the decision to select troponin. And I think that's all that's really required in the document that you're putting together.

The down-the-road document—you know, once you go through—we go through the troponin exercise, you're going to have to then do what Bill's committee has done, in a sense, and go back to the drawing board and decide, are there other ones there, and which ones would be the ones that would be most profitable? I like Bill's term, "the low-hanging fruit"—whether there are other low-hanging fruit that would be done.

But I think if we suggested to the working group that they do that now, that's probably going

to slow them down, don't you think? To add a big section on that to the present document?

DR. WALLACE: Yeah. I would like to minimize how much effort we commit within the document to discussing the next generation, if you will, of cardiac biomarkers. That more—the last two points were more points for the future activities of the working group, and not necessary for inclusion in the document.

The point—the information gaps, was does the NCSS want to engage the working group to take a lead role on identifying, devising paths forward—plans for filling those information gaps? Does the NCSS want to engage the working group in that activity.

And then the third point is just to affirm the understanding that the NCSS does want the expert working group to continue on the theme of biomarkers once the troponin document is complete, and engage the working group in discussions, much like Bill's group has done—alternative biomarkers, including the emerging technologies.

DR. DOULL: Right. And I think yesterday the comments from the members of the subcommittee were that we have a great team put together, and we

want that team to continue to work—they already have done all the leg work, and therefore it would be most efficient and—to just continue that process, so that—yes, Gloria?

DR. ANDERSON: I think it would be helpful, at least to me, if in your introduction you gave some background information on other—potential other biomarkers; no any in-depth discussion, but at least to put this in context.

DR. DOULL: Joy?

DR. CAVAGNARO: I'm sorry, I had a conflict yesterday—but, so, if we understand initially we set out that these two initiatives were priorities within the—based upon current regulatory hurdles, if you will—but there were some significant impact, in terms of moving forward.

And so would it be that once we identify these certain initiatives through this committee, that, in fact—and they've addressed the issue, that they somehow move on and other—other issues may then be considered.

I guess my concern is is that these becoming living groups, and then we then prevent—you know, resources, for example, would be key—that the issues that were brought up—you know,

like PET imaging—some of the newer technologies that I thought we were—shelved before, because we can only prioritize two.

I just want to make sure that, you know, we still, as a committee, have opportunity to introduce the newest and the key areas. And it would almost be like this would be their initiation, and then once they succeeded as a committee, perhaps they could somehow evolve into another—you know, graduate out of this committee, and somehow be supportive in some other initiative.

I don't know if that's clear. But, I mean, I just want to make sure that we don't lose, as a committee, what I think our charge is, is to keep our pulse on those areas where—may be constantly—you know, it might be changing, and may need—you know, we may need to set up another working group, etcetera. So I don't know --

DR. DOULL: Yes, I think the limitation of the groups we set up is they're focused—the cardiac group and the vascular group. So that it's only biomarkers which are related to those two areas, which they would be considering as alternative biomarkers.

There are other issues—you know, the omics

issue as a biomarker, the imaging issues as biomarkers and so on, are issues that the subcommittee as a whole needs to return to to see—you know, we decided to delay imaging because we didn't feel it was mature enough, really, to move into that area. We need, of course, to reevaluate that. And if that's changed, then we would need to do something appropriate.

I think we probably do need re-look at omics. I think we bypassed omics because we thought, gee, there's a lot of activity going on in that, and we'll be rediscovering the wheel to some extent. I'm not sure that's—you know, in retrospect that was the best decision. And we certainly need to re-look at that again.

Dan?

DR. CASCIANO: Can I comment?

DR. DOULL: Sure.

DR. CASCIANO: Well, we have to keep in mind that omics are just technologies and techniques. And so what we really should be focusing on are the biological questions, and not on the technologies that are available to answer the biological questions. And omics can be applied too any biological question that comes to this

committee. So I'm not sure if we should just focus on omics itself.

DR. DOULL: As a source of biomarkers.

DR. CASCIANO: Well, to me, omics are sort of like a spectrophotometer. And I don't think we—yeah, and it's more expensive. It's a tool that will help us answer the basic question that we have, and, in my mind, it's just a tool.

DR. SELKIRK: Just a couple of—to go a little further with the omics prospect. I think omics can do at least two things. One, it'll confirm biomarker placement in a pathway. In other words, it will tell you if you have a biomarker out in space, where that biomarker fits. Because things like micro-ray and proteomics will look at a lot of things at once, and then attempt to help you place that single biomarker in a pathway and sort of validate its—it will sort of validate its placement as a true biomarker.

But it also will help tremendously in discovery of biomarkers, because it can look at so many things at once, and build pathways that will evolve biomarkers with time.

So, yes, it's a tool, but the more data we build into it, the more knowledge we will have

coming out of it at the other end.

So we're in the early stages, but I think with time we'll see great acceleration, in terms of biomarker discovery and validation, using all the various omics that we are now beginning to have at our fingertips.

DR. DOULL: Yes, and hopefully, this committee would have a mechanism to keep our finger on some of those exciting things so that we would know the right time to step in and say, "Hey there's a tool that's potentially valuable in liver damage, for example, or whatever.

Does anybody have any other comments on the cardiovascular one?

Frank?

DR. SISTARE: I think some of the comments have been excellent with respect to sort of next steps, and we don't want to create an Expert Working Group to live in perpetuity, just because -- they've done a great job, we've got excellent people here, and it's a shame to disband them. But, clearly, the charge to this group was focus on biomarkers of tissue injury in the heart. And they've done a great job. And there's still work to be done. So we're premature, in terms of

talking about disbanding them. But, they are looking to the future. They can see an end to their work, and they're saying, "When we're done with us, what do you want us to do?" Okay.

The charge really is on CDER, I think, to answer that question. CDER needs to answer that question, go through their committee, and say—"We still have a problem"—okay—and figure out what the best way to deal with it. "We still have a problem with QT." We do, and we need to deal with that. Is this the best mechanism, or are there other mechanisms to do that? We have to figure that out.

We have another problem that has been brought to our attention with respect to the mechanical injury aspect of what you're saying. There's clearly a class or two of compounds that have surfaced, and then clearly a problem in clinical trials—some post-marketing indications of problems. Clearly the animal is showing these issues. You see it on histology. The question is, is there a biomarker? We could clearly use the expertise of this group to help us with that. Is that the most important pressing problem? We've got to go through a system to figure that out, you know.

Maybe—you know, there may be a system where the committee doesn't meet quite as often. You know, there may be—you know, the frequency of this particular committee meeting may go down to once a year, whereas vasculitis there's still a lot of activity. That was a much more immature problem, much more—a lot more effort needed to go into that, whereas troponin was a pretty mature biomarker. So meeting frequency enters into the thing as well, in terms of budget considerations.

So, these are important—very important things that need to be worked out.

What I'm hearing, you know, as Helen sets up this group, over on the CDER side, is that pharm tox community in CDER needs to communicate with them and say here are our needs, and make the case, you know, as you would in a court of law. We need to make our case and be really clear with it, and then let the chips fall where they may. It may say this committee in CDER may go to the NCSS and CTR and say, "We really feel that there's a need from some research to be done here," you know. That may be what happens.

But these are good questions. I don't think we're going to be able to answer them today.

I think—what I'm hearing, though—as a member on the CDER side of things—we need to be clear about getting some of these priorities addressed.

DR. DOULL: Yes, we were fortunate when we created these working groups, that we—we were lucky enough to get really first-class people to serve on both of these working groups.

And so—but, you know, as you change priorities, then that may require a different group of experts with different focus, and so on. So I think that's—that's what NCSS, in fact, has the ability to do, is to hopefully get the best experts to deal with a particular issue.

Just because it worked twice doesn't necessarily mean it's going to work again, Frank. [Laughs.]

DR. MacGREGOR: I think I would endorse what I think Joy and Frank are both saying, is that I think when both of these reports are final and come in to the subcommittee, that would be the time that the subcommittee should step back and take a look at the big picture, and the broad charge given to the subcommittee, which is where are the most fertile opportunities for collaborative science

that can really move things forward?

And I think it may be premature to decide where the cardiac tox group should go at this point, because we don't really have the assessment of the gaps and what really needs to be done. And I think probably you need to know where the committee really feels you should go, and the role that the committee should play in going there, to deal with those gaps on the very specific issue they were charged with, which was the biomarkers of cardiac injury.

And I think it's been—Bill said it's been about 18 months since the groups were formed, and it's probably been about two years since the subcommittee set its initial priorities. And a lot of new things have happened in those two years—new programs have been established at FDA. One of the areas that was discussed and decided not to pursue was hepatotoxicity, partly because there was a focus in ILSI and in other places at that time. But now NCTR has a new hepatotoxicity program, and new capabilities to bring some of the newer technologies to bear.

And so I think the committee really needs to reassess where the priorities should be reset

when these two reports are in and final, and decisions are made on how to follow-up on those recommendations.

Well, I think, Ken, in terms of our response to your—the working group, essentially those are the way would deal with those three issues pretty much. Is that adequate for—do you have other concerns to bring to us?

DR. WALLACE: The only—I'm sorry. The only other concern I have is one that was echoed by Bill, and that is, when we have this document that we want to publish in the peer review literature, is that we have to know what the policies are within the structure of the agency, as far as publishing them with some sort of approval by the NCSS, or if they should be done independently. We just need—are both looking for guidance back from the NCSS on that.

DR. DOULL: Yes, and I think our response to that is that, you know, we strongly encourage the publishing of the scientific paper, because we think it has great merit for the clinical—for the scientific community.

And we support the idea that the NCSS will, in fact, endorse that paper, and will be part

of it in the sense that that adds to the credibility, somewhat, of the whole process.

Now, the mechanics of that I guess we haven't fully explored yet. Jim tells us that there are certain hoops we have to go through in order to do that. And we'll explore that, to figure out how best we can do that in a way that helps you accomplish what you want to do, which is to put a paper out there that does, in fact, present the situation clearly.

Whether or not we may eventually have to have two publications—one which we would take to the Advisory Committee, for example, with a recommendation, as opposed to that one that's in the peer review literature, I think we have to explore that and figure out which is the best way to help you folks get the job done. And we'll do that.

DR. DOULL: Okay. The report that we heard this morning from Bill on the vascular side also raised another—other questions that the subcommittee needs to deutes so that our response is clear. And one of those had to do with the suppliers to the agents—or, the suppliers of those three compounds that you're concerned about.

And you said that you would draft that letter, and that the question, then, is whether those compounds should come to the Food and Drug and be distributed by Food and Drug, or whether there's some other mechanism which would be more preferable.

I gathered, from the discussion, that coming to Food and Drug seemed to be the method that would be most desirable. And I gather from Frank that there are some precedents for that, and some problems also with doing that. And so, clearly, we have to explore that, Bill, in order to be able to respond as to how best we can do that. And I think we'll do that. We'll find out what is the best way we can undertake that in a way that will help you all.

DR. KERNS: I think, then, that along those lines, that I'll finish drafting the letter as much as I can, and send it to the NCSS, and then we can fill in the details once we more clearly understand the MTA requirements and what flexibility the FDA has.

And I think we also mentioned that perhaps NCTR might be a home for distribution as well—something to consider.

DR. DOULL: We probably ought to do that a little more broadly, in a sense, because we're down the road talking about storage of samples, and collection of blood and what have you and so on. And, you know, we may need a mechanism that is, in fact, broader than simply distributing the dopamine or those three compounds, so that—I guess if there's some regulations, Jim, that hamper that in some way, we probably ought to know about that early on, because they may be different at NCTR, in terms of data—that storage.

DR. CASCIANO: There are some similarities, and there are some differences in here. I mean, we're a little bit more flexible than the product centers, because of the different mandates. But weearly we need to look into all those things, and we really shouldn't lose sight of what may be the simplest solution to the compound distribution. That is, we need to ask do we really need an MTA, or could the materials just be made available from the company that makes them. That might be the simplest to do, unless they have a problem with that.

DR. DOULL: Well, I was thinking, you know since we have an opportunity at the end of October

to talk to the Advisory Committee for Pharmaceutical Sciences, if there is some mechanism that would be facilitated by that opportunity we perhaps could ask the Advisory Committee to help us do whatever we're going to do.

But, hopefully, we would have some indication as to what we ought to do—by then.

Okay, the second thing, Bill—you talked about comments and responses to the White Paper, which you provided us with, and we gave you some this morning. I think, there again, we'll—these have gone out to the other members, to Jay Goodman and to Ray Tennant, and I'll get in touch with those—both of those members and add their comments to what we have from this morning's comments. And we'll then provide those to the working group, along with the thanks of the subcommittee for your—to both of you—your groups for the hard work that you've done, and for the fact that you've reflected glory on the intent of this whole effort.

If it had been a disaster, we'd have been in trouble. Instead, it's a superlative achievement, and we're delighted.

DR. KERNS: Thank you, John, and I'll communicate that to the people who did the work.

DR. DOULL: I guess I'm like Joy, I held my breath for a little bit. You know, we didn't know this was going to work out—gangbusters.

Okay. I have, in there, the justifications of the selection of the agents, and the selection of the four tests that you're going to do. And you said you would include something in there?

D--

DR. KERNS: Yep.

DR. DOULL: —and some justification for the specific biomarkers. You had that huge table, which listed them all. And then that was distilled down to the four that you selected. And, I guess, the question was exactly how did that process work?

DR. KERNS: Yes. Agreed. In addition, we will add the rat protocol. We will add some justification about how we chose the rat versus the monkey, etcetera.

And we will add some discussion on the incidence of the drug-induced lesions in humans. No problem.

DR. SISTARE: And I think, you know, Jim's suggestion is how big of a problem is this? Not just based on the human known angitis-type

reaction, but in terms off what we're seeing in terms of the animal—try to put a perspective on how big of a problem that is, and why is this an important thing to draw our intention to.

DR. KERNS: That's no problem.

DR. DOULL: Is there—Frank, is there data on the—why compounds or new drugs are rejected? The most prevalent --

DR. SISTARE: The only data you get out of the FDA is why drugs are pulled off the market. We often don't know why drugs are stopped—why developed gets stopped by sponsors. And a lot of times that decision is made by them—they decide to not pursue a particular candidate, and that information isn't always shared. We can make guesses, but that information isn't always shared. And there's a lot of complex decisions. They go into that.

So FDA could not provide that information. The only information we could provide is when a drug is pulled off the market, why. But why a drug is stopped in a Phase II, or Phase I or a Phase III trial, we don't always know why.

DR. DOULL: And you hear that all the time—that 80 percent of the new drugs somehow go

down the toilet.

DR. SISTARE: Right. We know the numbers—we know the numbers. We don't know the reasons behind them, though, always. And that would be beautiful. We'd love to have that information, you know. There's—I don't know—I just don't know of any definitive source for that information. We'd love to have that information.

DR. MacGREGOR: You know, PhRMA has published that kind of information, but in very broad categories, like things that have failed due to economic considerations versus drug toxicities and so on. But I'm not sure it's been ever done in terms of specific causes of toxicity—failure due to specific toxicities.

DR. DOULL: I'm just thinking, as a front end for these papers—you know, that certainly would be a lead-in, because it would say Food and Drug—you know, we're wasting a lot of money. We're wasting a lot of effort. We're doing a lot of redundant studies and so on. Certainly, we ought to figure out a way to do it better if we could.

You had mentioned, Bill, also the need for the NCSS to do some future planning. And we agreed, that's a charge that we'll take, and try

and figure out, with—in conjunction with the working groups, how best to bring this information out.

We have a lot of information which would be of great use and value to the scientific community out there, and the question is whether a workshop would do that—a small workshop focused on one of these problems, or a larger workshop focused on biomarkers—how best to do that.

DR. KERNS: Well, that would be very helpful, I think—receiving that directive to Ken and myself. It would be very clear, then, what we needed to be doing. It would be very helpful.

DR. DOULL: Yes, I would think the working groups could advise us as to where --

DR. KERNS: Sure.

DR. DOULL: —they think it would be most helpful --

DR. KERNS: Yep.

DR. DOULL: —you know—we're happy to do that, too.

DR. CAVAGNARO: Can I just make a comment?

Jim—since Jim is currently or outgoing chair of the PhRMA drug safety committee, can you discuss, you know, the—whether or not this

initiative has been discussed in a broader forum, amongst all the member companies and, you know—and the support and enthusiasm, or—of the—group?

DR. GREEN: Sure. Yeah.

Well, I think both—there's a high degree of awareness amongst—let's see, there's 15 member companies that are on the Drug Safety Steering Committee of both of these initiatives, as well as the committee's activities.

So, speaking on their behalf, and reflecting my own opinion, I think they would be remarkably impressed. I think what—the questions would remain, especially with the pending changes within the advisory committee structure in Pharmaceutical Sciences, and the creation of a tox path group in that, is an understanding of the logistics into how—and particularly these areas where new technology is producing potentially decision-making data sets, or may be viewed as decision-making data sets by those folks that are reviewing our applications. And if you have several hundred reviewers, in several divisions, it's very easy for there to be mixed impressions about the state of readiness of a particular new technology, a new approach, a new marker, etcetera.

So I think, to the extent that this kind of committee, in addition to the new evolving advisory committee structure can have some kind of influence, and sponsors can see that, with respect to communication of points of science and interpretation that affect the day-to-day review, I think there would be remarkable support.

Easier said that done, though.

DR. SISTARE: Along that line, I will just mention one event—one thing happening in CDER. CDER has formed two committees, for example, focused on pharmacogenomics and toxicogenomics—a clinical and a nonclinical committee—to coalesce a consensus thinking, in terms of should a sponsor choose to submit such data, you know, how would we want that? You know, that kind of thing. And that's something that will allow us to generate internal thinking—internal consensus—but then having this mechanism allows us to externalize our thinking and get some feedback on that.

So, I would just add that, in terms of the new technologies and how to get reviewers tuned into a consensus, in terms of how it should be approached across the different review divisions, it is important to have that internal committee,

and then to have a place where we can interface with PhRMA on that.

And one could potentially see, you know, that we have a problem with standards. And then we need to go to the NCSS, through NCTR, to help with standardization. That may be an issue. There may be some experiments that need to be done. I don't know.

But I think having the matrix, having something in place really, I think, helps—helps the process. And I think we're going a long way toward that.

DR. DOULL: I think, actually, when this subcommittee was created, that kind of was the hope that, you know, we would find—it seems logical, in a sense that, you know, having the group looking at biomarkers which would contribute nonclinical and bridging markers and so on—all that makes good sense.

I think when the committee was formed—or subcommittee was formed, we had no real idea of the complexity of forming subcommittees, particularly one that's doing this kind of activity, because it's somewhat different than activities have been done before. So, you know, ienjoy some of the

results of all that experience. And, hopefully, we're going to move in the direction you're talking about, Jim.

Ah—let's see, the only thing I had written—else written down, Bill, was the timeline thing that Joy raised, and you also said that would be part of your report. For the timeline of those effects, and in animal studies?

DR. CAVAGNARO: Right.

DR. DOULL: She was asking about, you know, how long it takes in a rat?

DR. KERNS: Time to injury.

DR. CAVAGNARO: Right.

DR. DOULL: Yeah. I guess the inter-species argument also would be something that should be mentioned there, because the dogs—as I recall what you were all saying—the dogs don't totally replicate the rat stuff. Well, at least you need to talk about that in the report.

Have we got other issues, Bill, that the subcommittee needs to address?

DR. KERNS: No. I'm happy.

DR. CAVAGNARO: So—one more question. So there will be this protocol—the rat protocol—with the various—you know, the four areas that have been

discussed. And then you mentioned the fact that there are ongoing activities.

Who is capturing. You know, it's not your charge, but who will be capturing the overall data base, if you will. So there's the NCSS initiative and then, clearly, companies—I mean, we heard that—Calvert—oh, Astra-Zeneca, is going to do some --

Now, I mean, when—I presume that those initiatives, when we have the October symposium or workshop, that would be a forum for others, you know, engaged in this area to present. Is that what you're envisioning?

DR. KERNS: That's my hope.

DR. CAVAGNARO: Yeah.

DR. KERNS: Once again, it is their choice—to share or not to share. But my hope is to, over the next 12 months, to interact with, you know, the companies doing work independently. And, hopefully, we can share at the table. And I think—we've already initiated that process, and it's worked quite well so far. So I would anticipate that will continue and culminate in a symposium sometime next year—next fall, where people will formally share these data.

As far as capturing and organizing, collecting and collating, I think, for the people doing independent work, that will come from their publications, and we'll see it once it's published.

DR. SISTARE: Actually, it raises a very good point. Maybe this might be an opportunity to try to capture a conference proceedings. You know, like, maybe get Tox Path interested in maybe publishing the proceedings. That might be a really nice way to capture everything and really encourage some of the individual investigations going on to bring it to a point of fruition, where it can be shared.

Sometimes a stumbling block is you're working with a compound that you can't put the structure—you know, you can't cite it, you can't put the structure in. We always have to figure out how to do that. That's always a problem. But there's probably some way of doing it. We just have to figure it out.

DR. DOULL: At our last meeting you raised the issue about confidentiality of results and how that was being handled amongst the various members of the group. And you didn't bring that up this time, and so I gather you're—the methodology that

you developed for that is --

DR. KERNS: Well, we've agreed amongst the members sitting around the table that everything we do will be in the public domain.

DR. DOULL: Okay.

DR. KERNS: And I think when we contact our—the suppliers of Fenoldopam and Abbot, the PD-IV inhibitor, I think we need to make the same agreement, or put the same words in that letter so that, you know, there's nothing proprietary will surface out of this.

And we need to make it clear, as we distribute compound, that the—you know, the other customers understand the rules here. Because that's the way that we circumvented this issue, of creating intellectual --

DR. DOULL: I recall we had no easy answer to that problem. So—[laughs].

DR. KERNS: Well, that's what we decided—that's what would be easiest. It won't happen—theoretically.

DR. DOULL: That's an old adage. If you out wait the problems they go away—a dean's adage.

Any other arguments, comments or suggestions?

Yes—go ahead, Gloria.

DR. ANDERSON: Mr. Chair, as we move to what I perceive to be a different level, having gotten these two reports, and having given some instructions as to how they should proceed, it might be a good time to look at the background paper that we received when the committee was formed, and review the objectives that were set forth and see where we are, and perhaps either get some guidance from the advisory committee, or give them some recommendations on how we might proceed, beyond these two papers.

DR. DOULL: I agree. And since that—the next Advisory Committee on Pharmaceutical Sciences is scheduled for October 21st and 22nd, and Jim and I will give some thought to that specific mandate for our subcommittee, and also to report on the progress of the two working groups.

[Pause.]

All right, we heard the recommendations by Helen on the reorganization of the advisory committee, and I think—you know, other than commenting on the fact that for the subcommittee we're delighted with the fact that she's going to maintain the link to the regulatory recommendation

pathway. It's premature, really, to get into that too much because we don't know exactly, other than what she told us will happen.

I think, Jim, we need to be sure that the members of the subcommittee are fully informed about what happens in the October meeting.

DR. MacGREGOR: Mr. Chair, with regard to the October meeting, I might encourage the subcommittee to complete your review of these documents, if possible, and to be able to go to that committee with a—you know, a clearly formed view of the subcommittee that, hopefully, could be endorsed by the parent committee at that point, so that endorsement could go back to the working groups.

DR. DOULL: Yes, we willo that we will be able to bring those to the advisory group if we have additional things.

And Gloria and I—you're going to be at the October meeting. Yes—we'll be there. So, hopefully, if there are questions about the working groups or where we're going and so on, we'll be able to respond to those.

DR. CAVAGNARO: [Off mic.]

DR. MacGREGOR: You're aware of the date?

guess I would like to formally go on record with my compliments to the two working groups. I think they've made tremendous progress and I think the outline in the report really show the fruits of a lot of labor that went into those. So my thanks—my thanks to them for a job well done.

DR. DOULL: We are adjourned.

[Whereupon, at 11:18 a.m., the meeting was adjourned.]

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CERTIFICATE

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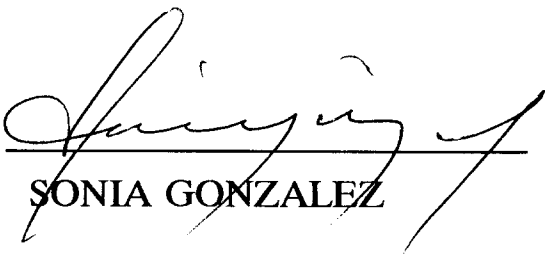

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