

FOOD AND DRUG ADMINISTRATION

NONCLINICAL STUDIES SUBCOMMITTEE

OF THE

ADVISORY COMMITTEE FOR PHARMACEUTICAL SCIENCE

8:05 a.m.

Tuesday November 13, 2001

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Conference Room
5630 Fishers Lane
Food and Drug Administration
Rockville, Maryland 20857

ATTENDEES

SUBCOMMITTEE MEMBERS:

JOHN DOULL, M.D., PH.D., Chair
Professor Emeritus of Pharmacology and Toxicology
Department of Pharmacology and Toxicology and Therapeutics
University of Kansas Medical Center
3901 Rainbow Boulevard
Kansas City, Kansas 66160-7417

KIMBERLY TOPPER, Acting Executive Secretary
Advisors and Consultants Staff
Center for Drug Evaluation and Research
Food and Drug Administration (HFD-21)
5600 Fishers Lane
Rockville, Maryland 20857

GLORIA L. ANDERSON, PH.D., Consumer Representative
Fuller E. Callaway Professor of Chemistry
Morris Brown college
643 Martin Luther King Jr. Drive, N.W.
Atlanta, Georgia 30314-4140

JOY CAVAGNARO, SGE Consultant
P.O. Box 1362
Leesburg, Virginia 20177

JACK H. DEAN, PH.D., D.A.B.T., Industry Participant
President and Scientific Director
Sanofi-Synthelabo Research Division
International Director Preclinical Development
Sanofi-Synthelabo, Inc.
9 Great Valley Parkway
Malvern, Pennsylvania 19355

JACK H. REYNOLDS, D.V.M., Industry Participant
Vice President, Drug Safety Evaluation
Pfizer, Inc.
50 Pequot Avenue
New London, Connecticut 06340

DAVID M. ESSAYAN, M.D., Government Participant
Food and Drug Administration
CBER/OTRR/DCTDA/PTB, HFM-579
Woodmont Building 1, Room 200 N
1401 Rockville Pike
Rockville, Maryland 20852

ATTENDEES (Continued)

SUBCOMMITTEE MEMBERS: (Continued)

JAMES T. MacGREGOR, PH.D., D.A.B.T., Government Participant
Deputy Director for Washington, NCTR
Parklawn, 16-53 HFT-10
5600 Fishers Lane
Rockville, Maryland 20857

HELEN N. WINKLE, Government Participant
Acting Director, Office of Pharmaceutical Science
Food and Drug Administration
CDER/OPS/HFD-003
Woodmont Building 2, Room 6008
1451 Rockville Pike
Rockville, Maryland 20853

GUEST PARTICIPANTS FOR NOVEMBER 13, 2001 MEETING:

KENDALL B. WALLACE, PH.D., D.A.B.T., NCTR Committee
Representative
Professor, Department of Biochemistry & Molecular Biology
University of Minnesota
School of Medicine
Duluth, Minnesota 55812-2487

GORDON HOLT, PH.D., Invited Industry Participant
Principal Scientist
Oxford GlycoSciences
4 Sparrow Valley Court
Montgomery Village, Maryland 20886-1265

THOMAS PAPOIAN, PH.D., Government Participant
FDA/CDER/ORM/DACADP, HFD-170
Parklawn Building 9B-45
5600 Fishers Lane
Rockville, Maryland 20857

ELIZABETH A. HAUSNER, D.V.M., D.A.V.T., Government
Participant
FDA/CDER/ORM/DCRDP, HFD-110
WOC 2 Building, Room 5060
1451 Rockville Pike
Rockville, Maryland 20852

ATTENDEES (Continued)

GUEST PARTICIPANTS FOR NOVEMBER 13, 2001 MEETING:
(Continued)

DR. FRANK SISTARE, Government Participant
Director, Division of Polypharmacology Research
FDA/CDER

ALSO PRESENT:

DR. JOE DeGEORGE
FDA/CDER
Chair, Pharm Tox Coordinating Committee

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P R O C E E D I N G S

(8:05 a.m.)

1
2
3 DR. DOULL: I think we can go ahead and start.
4 As I'm sure all of you know, this is the meeting of the
5 Nonclinical Subcommittee of the Pharmaceutical Science
6 Advisory Committee.

7 The purpose of our meeting this morning is
8 twofold really. First, we need to get a progress report
9 from the working groups which we have established, and
10 second, we need to facilitate the arrangements to support
11 these groups and to keep track of what they are doing.

12 Why don't we go ahead, Kimberly, and do the
13 security thing first, and then we can go around the room.

14 MS. TOPPER: The following announcement
15 addresses the issue of conflict of interest with respect to
16 this meeting and is made a part of the record to preclude
17 even the appearance of such at the meeting.

18 Based on the submitted agenda and information
19 provided by the participants, the agency has determined
20 that all reported interests in firms regulated by the
21 Center for Drug Evaluation and Research present no
22 potential for a conflict of interest at this meeting with
23 the following exceptions.

24 In accordance with 18 U.S.C., section
25 208(b)(3), waivers have been granted to Dr. John Doull, Dr.

1 Gloria Anderson, Dr. Jay Goodman, Dr. Joy Cavagnaro, and
2 Dr. Kenneth Tindall that permit them to participate fully
3 in today's discussions.

4 A copy of these waiver statements may be
5 obtained by submitting a written request to the agency's
6 Freedom of Information Office, room 12A-30 of the Parklawn
7 Building.

8 We would also like to note for the record that
9 Dr. Gordon Holt, Oxford GlycoSciences; Lester Schwartz,
10 D.V.M., GlaxoSmithKline; Williams Kerns, D.V.M., Pharma
11 Consulting; Jack Dean, Ph.D., Sanofi-Synthelabo; and Jack
12 Reynolds, D.V.M., Pfizer Global Research and Development
13 are participating at this meeting as industry
14 representatives acting on behalf of the regulated industry.
15 As such, they have not been screened for any conflicts of
16 interest.

17 In the event that the discussions involve any
18 other products or firms not already on the agenda for which
19 FDA participants have a financial interest, the
20 participants are aware of the need to exclude themselves
21 from such involvement, and their exclusion will be noted
22 for the record.

23 With respect to all other participants, we ask
24 in the interest of fairness that they address any current
25 or previous financial involvement with any firm whose

1 product they may wish to comment upon.

2 Thank you.

3 DR. DOULL: Any comments on the conflict of
4 interest?

5 (No response.)

6 DR. DOULL: Why don't we go around the room
7 then just so everyone knows everyone. Ken, why don't we
8 start over there with you, who you are and where you are
9 from.

10 DR. WALLACE: I'm Ken Wallace, Professor of
11 Biochemistry and Molecular Biology at the University of
12 Minnesota School of Medicine in Duluth.

13 DR. HOLT: I'm Gordon Holt. I'm Principal
14 Scientist at Oxford GlycoSciences.

15 DR. REYNOLDS: I'm Jack Reynolds, Senior Vice
16 President of R&D from Pfizer.

17 DR. DEAN: I'm Jack Dean. I'm responsible for
18 preclinical development for Sanofi-Synthelabo.

19 DR. DOULL: John Doull, University of Kansas
20 Medical Center.

21 DR. CAVAGNARO: Joy Cavagnaro with Access Bio
22 in Virginia.

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

25 DR. MacGREGOR: I'm Jim MacGregor. I'm the

1 Deputy Director of the FDA National Center for
2 Toxicological Research.

3 DR. ESSAYAN: David Essayan, Center for
4 Biologics, Food and Drug Administration.

5 DR. HAUSNER: Elizabeth Hausner, Division of
6 Cardioresenal Drug Products, Food and Drug Administration.

7 DR. PAPOIAN: Tom Papoian, a pharmacologist,
8 Center for Drugs.

9 DR. SISTARE: Frank Sistare, Director of the
10 Division of Polypharmacology Research in the Center for
11 Drugs, FDA.

12 DR. DOULL: Thank you.

13 Why don't we go ahead then. Our plan for this
14 morning is we are not going to follow this agenda tightly
15 since it's fairly flexible. As I indicated, we want to
16 hear from the working groups, where they are and what they
17 have been doing, and then we want to close by spending a
18 little time figuring out how best we can help the working
19 groups in accomplishing the goals that have been set out
20 for them by this committee.

21 So, why don't we start with the cardiology.

22 DR. WALLACE: I'm real pleased to report back
23 to the NCSS that the Working Group on Biomarkers for
24 Cardiac Injury has, in my opinion, been very productive.
25 There is certainly a lot of enthusiasm and commitment

1 shared by the members, and it is a real pleasure working
2 with this group.

3 Since the last time that we reported back to
4 the NCSS, we have really focused on a meeting that occurred
5 last week with the American College of Toxicology. So,
6 what the working group did is that we met once here at the
7 agency on October 12th, and it was basically a pre-meeting
8 planning session where two of the speakers presented their
9 science and then we spent the rest of the day just
10 preparing for exactly what was going to transpire during
11 this meeting where our group was invited by the American
12 College of Toxicology to conduct a symposium on the topic
13 of the troponins as biomarkers of drug-induced cardiac
14 injury. So, we spent that day doing that.

15 We then met in downtown D.C. at the Renaissance
16 Hotel the day of our symposium, which was last week,
17 November 6th. It was an afternoon symposium. We had a
18 morning session, and again we really wanted to maximize the
19 amount of information that we gained from that venue where
20 we had an opportunity to get feedback from the audience on
21 the topic at hand. So, we met in the morning to strategize
22 exactly how we were going to conduct the afternoon session
23 with that in mind.

24 We then had the afternoon session where we had
25 a series of, I believe it was, four or five presentations.

1 The program from the American College of Toxicology meeting
2 is included in your handout. There was one substitute
3 speaker. I will point that out to you. So, we had that
4 symposium.

5 Then we ended the symposium with, I thought, a
6 very engaging dialogue, a question and answer period
7 afterwards where the panel responded to a lot of questions
8 from the audience on the topic, and I found that to be very
9 helpful.

10 We then met the following evening and had a
11 working dinner meeting where we then planned what we were
12 going to do with that information. We planned our path
13 forward. We concluded where we were and we decided what
14 the next steps were going to be.

15 So, at this moment, what is currently happening
16 within the expert working group for the biomarkers of drug-
17 induced cardiac injury is that we are currently preparing a
18 document that is suggesting that the troponins I and T are
19 useful bioindicators, biomarkers, of drug-induced cardiac
20 myocardial cell injury. We are just at the beginning
21 stages of writing this document.

22 Now, it is very important that when we write
23 this document, it is going to contain all of the elements
24 that were outlined and presented last time, as far as what
25 are the characteristics of an ideal biomarker. So, it is

1 very important to understand that what these biomarkers,
2 the troponins, mark is cell injury. They don't mark
3 anything other than that. Active cell injury. They don't
4 mark an infiltrative type of cardiac injury. They don't
5 mark a congestive cardiac injury or an electrical
6 malfunctioning of the myocardium. It's a cell membrane
7 injury type of phenomenon. So, we are currently writing
8 this document, have just begun the initial stages of
9 writing this document as of last week.

10 In the process of writing this document, we are
11 going to make sure we not only understand what type of
12 cardiac cell injury or cardiac injury that we are marking,
13 but also the kinetics of that marking, how rapidly this
14 bioindicator is released to the serum, and then how rapidly
15 it returns to normal values following the act of injury
16 event.

17 But we also are addressing an issue that we
18 think is important; that is, is there a relationship, a
19 quantitative relationship, between the amount of troponin
20 that is released to the serum and the amount of damage that
21 has occurred to the myocardium? So, the data that we've
22 looked at gives us an indication of what that relationship
23 may look like, but the evidence is not as strong as we
24 would like it to be in order to suggest it as a working
25 document. So, another subcommittee of our working group is

1 | designing an ideal experiment that would address the issue
2 | of whether there's a quantitative relationship between
3 | serum troponin levels and the degree of cardiac injury so
4 | we can extrapolate on a dose or time course kind of a
5 | basis.

6 | Then as we are doing that, we are also keeping
7 | on our radar screen the fact that we want to mark other
8 | types of cardiac injury. So, we are looking at other small
9 | molecules and biomolecules as biomarkers of other types of
10 | cell damage, whatever they may be. So, we have another
11 | group of us who are looking at the horizon and looking at
12 | what are we going to do in the next stages. The next
13 | stages I think are going to be very exciting.

14 | First of all, let me just say that troponins
15 | offer a great opportunity in that they are ideal in the
16 | sense that they do cross platforms. The homology of the
17 | troponin sequence is such that we can use the same
18 | technology to mark myocardial cell injury in a variety of
19 | different experimental species as well as humans, and so
20 | this biomarker will have the characteristics of being able
21 | to be used to bridge across the nonclinical/preclinical
22 | studies to clinical and surveillance types of studies as
23 | well. So, we are real pleased with that.

24 | Along the same line, it is our opinion -- and
25 | we will work this out in the document -- that the troponins

1 | may be more effective at marking cardiac cell injury than
2 | any other biomarker that is currently being used to mark
3 | the same type of event. But we are in the process of
4 | developing that argument.

5 | We're real excited about getting into the next
6 | stages, the more challenging stages of describing other
7 | types of cardiac injury and then discussing what kind of
8 | markers that may be most useful in marking those events,
9 | whether it be the infiltrating, inflammatory pericarditis
10 | kind of a thing or what have you, but also looking at the
11 | emerging technologies of the biotechnologies, gene arrays
12 | and proteomics and such, and looking at the possibilities
13 | of whether those offer opportunities to employ those
14 | technologies as well in marking cardiac injury. But we are
15 | really looking several months down the road before we'll be
16 | able to really engage or invest ourselves in those
17 | discussions. But we're excited about that.

18 | So, that concludes my presentation. I would be
19 | very happy to answer any questions or expand on any of the
20 | information that I presented.

21 | DR. DEAN: Ken, will this document being
22 | prepared by your group compare the sensitivity against the
23 | classic CK and LDH, transaminase, et cetera and time course
24 | of the conventional markers versus troponins?

25 | DR. WALLACE: The intent is to do that. It is

1 | my objective that in the process of recommending that the
2 | troponins be used, we do it on a comparison basis, that it
3 | be used instead of or in lieu of other classic biomarkers,
4 | not in addition to, unless in the process we can define how
5 | one of the other biomarkers pick up something of importance
6 | in the whole process that the troponins miss. But
7 | everything is going to be done on a comparative basis.

8 | DR. DEAN: But both in specificity and
9 | sensitivity, the troponins look superior to the more
10 | conventional biomarkers?

11 | DR. WALLACE: Yes. From the evidence that
12 | we've seen so far, it looks very promising.

13 | DR. CAVAGNARO: Have you talked about how one
14 | would integrate this into a conventional development
15 | program, for example, as part of safety pharmacology or
16 | single-dose/repeat-dose studies or screening versus
17 | mechanistic? How would one then try to introduce this into
18 | a development program?

19 | DR. WALLACE: Well, the committee has not
20 | discussed that extensively, Joy. It is all going to depend
21 | upon the application, the intentional use of the drug.
22 | What the committee has suggested is that the troponins will
23 | not necessarily be promoted for use as a standard drug
24 | screen, but in those cases where there's reason to suspect
25 | that there might be a cause for concern for drug-induced

1 cardiac injury, that the troponins might be pursued at that
2 point in time, but only if there's a basis for a concern.

3 DR. DOULL: Let me ask Ken. One of the goals
4 of this subcommittee is to look at preclinical tests and
5 then evaluate their ability to be carried on over into the
6 clinic. I gather you guys are also focusing on that
7 potential?

8 DR. WALLACE: Yes, we are and we are very
9 encouraged that the troponins are being used clinically
10 now. They are approved clinically now as biomarkers of
11 ischemia reperfusion injury. So, we already have clinical
12 evidence for this.

13 DR. DOULL: So, this paper you are going to do
14 then would talk both about the preclinical and the clinical
15 and efficacy and so on.

16 DR. WALLACE: If that is what you wish it to
17 talk about. I'm not certain in that we've just begun to
18 put our pen to paper, but if that's certainly something
19 that you would like to have in the document, we'll make
20 sure that it's there.

21 We weren't going to do an exhaustive review of
22 the clinical literature, I don't believe. But we're going
23 to talk about the promise that the troponins have and that
24 there is already a lot of clinical evidence out there that
25 suggest that they're equally effective in marking clinical

1 myocardial cell damage. So, if you would like us to
2 emphasize that in the paper, we'll add more emphasis to it.

3 DR. DOULL: I think Jack has already touched on
4 the business about efficacy. You need to say something
5 about how the troponins compare with other myocardial
6 markers, and then hopefully you would say something about
7 this is a preclinical test that also has clinical
8 application.

9 DR. WALLACE: Right.

10 DR. DOULL: Both of those are charges that we
11 need to carry back to the advisory committee.

12 Are you guys thinking of publishing it? What's
13 the future of your document?

14 DR. WALLACE: Well, I'm a big advocate of
15 publishing, but I am trying to learn what restrictions and
16 what parameters are put around the working group by the
17 NCSS. At some point, I would like to see it published.

18 DR. DOULL: That's certainly something I think
19 we need to talk about because that's our charge as to how
20 we can help you, and that is certainly something, Jim, we
21 need to give some thought to.

22 DR. WALLACE: My plan would be to charge ahead
23 with the intent of publishing until I was told to hold up.

24 DR. CAVAGNARO: Certainly the data. The
25 challenge becomes then in terms of recommendations. So,

1 clearly all the data that you accumulated is very important
2 in support of that, and whether a separate piece can be
3 done in terms of making recommendations now, because this
4 has, of course, huge global ramifications in terms of
5 suggesting new parameters into development programs in the
6 theme of harmonization. But I think clearly the data that
7 you accumulate is very important that it be published to
8 get out there.

9 DR. WALLACE: Right, and at this point in time,
10 I believe all the data that we are reviewing is publicly
11 available, and so we are not using any proprietary
12 information that we are drawing our conclusions from. So,
13 absolutely.

14 DR. CAVAGNARO: But that won't preclude it
15 because I thought that there was some -- because it was
16 important to get original proprietary data, you could
17 somehow blind it. Wasn't that the charge, that people
18 amongst the groups felt comfortable in presenting?

19 DR. DOULL: Yes. We discussed that at the last
20 meeting actually, and the concern that some had was that in
21 addition to the literature data, for example, you might
22 very well have data from some of the companies, for
23 example, that would be confidential, and how would that be
24 handled in terms of writing a report or making that data
25 available. We didn't really resolve that. We recognized

1 that that was a problem. As I recall, we had no up-front
2 solution to that, except to the point where you can get it
3 into a review kind of document that you can publish. Then
4 that makes it, of course, available as Joy says.

5 DR. WALLACE: The committee has talked briefly.
6 Again, we are real early in the phase of writing this
7 document. So, we don't know where we're going to come up
8 against a block where we have this issue arise, at which
9 point we'll have to address it.

10 The committee has talked about whether we want
11 to go to other organizations to help generate and share
12 information that is not yet public. But at this moment, as
13 of last week, the committee felt that there was sufficient
14 evidence available that we don't have to engage other
15 organizations at this point.

16 DR. DOULL: Let me ask Jim. Are you aware of
17 any constraints that we need to consider here in making
18 this data public and so on?

19 DR. MacGREGOR: I don't think I'm aware of any.
20 I think that the scientific aspects of the information
21 pulled together could be published, and I don't see any
22 limitations to that except for the normal issues of any
23 proprietary data that might have been considered in getting
24 appropriate consent or protecting that if that becomes an
25 issue.

1 Since I have the microphone here, I guess one
2 thing I might put out on the table is I think that now is
3 kind of a critical point for this committee, which has now
4 met several times and themselves gone over in fair detail
5 in their committee the data on the troponins and, to a more
6 limited extent, the comparison with other markers. But I
7 think the committee, now that it has made a decision that
8 it is itself convinced of the value of troponin as a flag
9 for injury and that they're going to go ahead with the
10 paper, one of the questions might be how this group sees
11 their interaction with the expert group during the
12 development of that. So, the committee is going to go off
13 and write a document.

14 And I guess the question in my mind would be
15 would you like to see a presentation of the scientific data
16 here in this subcommittee and at what stage? I'm sure at
17 some stage you would. Would you like to have the draft all
18 done, read it, and then see the data, or would you like
19 some interaction as it's developed? Or how would you like
20 to see that development go?

21 DR. REYNOLDS: Well, I think some dialogue and
22 interaction, as the paper evolves, would be very important.
23 Many of us I think can have some insight into what should
24 be done or where you should go and how it can be leveraged
25 into practice.

1 DR. SISTARE: I think we should give the expert
2 working group a question to answer. Some questions have
3 been raised. Ken made the statement and it was a
4 conservative one, but I think maybe we should ask and
5 challenge the expert working group. Ken made the statement
6 that when cardiac injury is suspected, to then look and
7 measure for cardiac troponin T or one of the cardiac
8 troponins as a measure. The question that has been bandied
9 around is, is it better than some of the traditional
10 markers? So, that's a good question to have them focus in
11 on.

12 But another question that has come up in the
13 deliberations is, why not make it a part of the routine
14 clinical chemistry that's measured if we feel it can pick
15 up things that are difficult to see? Unless you happen to
16 make a slice through the heart and do some histopath and
17 just happen to catch a focal lesion, there's a chance you
18 might miss something like that. That's come up. So, I
19 think that might be a charge to challenge the expert
20 working group.

21 I guess we have to be careful. We have to not
22 ask for recommendations but ask for data, data that would
23 ask the question are there times when a routine measure of
24 one of the cardiac troponins would give a superior insight
25 into the cardiotoxic potential of a compound as if you

1 | didn't do it. Or would it be a waste of time and money and
2 | resources to do it routinely? If we can develop some data
3 | lines along that.

4 | The other point that has come up is clearly
5 | Malcolm York presented some data with anonymous compound
6 | names where they looked at cardiac troponin and showed the
7 | real benefit in a lot of those cases where cardiac troponin
8 | measurements really helped them decipher what was going on
9 | with their particular compounds, whereas CKMB or the LDHs
10 | didn't do it.

11 | My guess is, from talking to some of the other
12 | researchers in some of the other companies, they have
13 | incorporated troponins into some of their studies. And I'm
14 | wondering if the expert working group put a call out to
15 | sponsors doing these kinds of studies if they wouldn't be
16 | able to share data similar to what Malcolm shared that
17 | could be incorporated into a very extensive analysis of
18 | this question.

19 | DR. ESSAYAN: Pursuing some of the questions
20 | that Frank just raised begs the question of what the
21 | stability of the assay would be over time and the
22 | reproducibility in normal, unmanipulated animals of various
23 | species. If we're going to go in the direction that Frank
24 | just outlined, that would be an important data set as a
25 | comparator to know the distribution characteristics of the

1 normal values and then that would play into the
2 quantitation question that you raised earlier.

3 DR. WALLACE: The committee has seen one data
4 set that addresses both of those questions, the variability
5 of the troponins in an otherwise control animal, as well as
6 the stability of the troponins on storage.

7 DR. HAUSNER: Both David and Frank raised very
8 important points, and I'm not going to reiterate what Ken
9 just said about the kinetics of the troponins. But what
10 Frank suggested I think is very important, and it was
11 briefly touched upon in some of the discussions, that there
12 seem to be two possible scenarios for use of the troponins.
13 I guess the question is which one or do both increase the
14 safety for participants in clinical trials the most. One
15 could be where you have a suspicion of cardiotoxicity maybe
16 because of other members of the class of drugs. The other
17 scenario is a drug of unknown history, perhaps new in a
18 class, and would you increase the safety more for clinical
19 trial participants to have troponins in that case as a
20 routine part of the screening? And I agree with you,
21 Frank, that that would be very important to address.

22 DR. CAVAGNARO: I want to say about five years
23 ago, but it could be longer, there was an initiative by the
24 Association of Veterinary Clinical Pathologists. It was
25 championed by Kurt Wyngard and Jack Bloom who is now in

1 clinical. I know presented for CBER and there were
2 presentations from CDER and maybe other FDA centers. The
3 purpose of that meeting was to explore different analytes
4 in terms of standard clinical pathology measurements.

5 I am wondering if you've had discussion with
6 them or during this discussion -- because this is where
7 you're going in terms of incorporating -- whether or not
8 touching back with them or maybe there is somebody in your
9 group that liaises with some of those folks. But I think
10 to get the veterinary clinical pathologists involved at
11 some point I think would be quite useful.

12 DR. SISTARE: Yes, I agree with that totally.
13 Malcolm York, who is on the expert working group, was on
14 that committee as well, and I challenged him with that
15 question. You know, you guys five years ago published a
16 paper, and for routine animal studies, you suggested these
17 10 or 15, whatever markers. You didn't include a real
18 specific cardiac injury marker in that set. Let's talk
19 about that. And would you revisit that now in light of all
20 the information you've gathered? What do you think? And
21 he really hemmed and hawed. He wasn't completely sure. He
22 was still leaning on routine testing, probably not
23 incorporate it, still save it for when you suspect it. But
24 there was a challenge and there was a dialogue, and I still
25 think it's something that needs to be resolved and more

1 | carefully thought through.

2 | But I agree we may need to broaden it perhaps.
3 | I don't know if we have to broaden it or how we can dictate
4 | this or what. I'm not sure how the whole process works,
5 | but I do think that we do need to get a broad perspective
6 | on this and get real dialogue if we feel that everything is
7 | telling us this should be routine.

8 | DR. DOULL: Yes, that's clearly one of the
9 | questions. Where do you position this in terms of it being
10 | the most useful? Early on as a preliminary screen? It
11 | doesn't sound like that. It sounds like later on when you
12 | have some clues to bring it in.

13 | Looking through this paper, Ken, it seems to me
14 | that that did, in fact, cover several areas. I guess in
15 | terms of publication, I think it's better to have this out
16 | in the real world, what the working group is doing, rather
17 | than just present it here. We're going to have to take
18 | your information and present it to the advisory committee
19 | to show what we're doing and why it's important and all.
20 | But this needs to be out widely distributed in order that
21 | everyone is aware that we're concerned about cardiotoxic
22 | assays that are predictors of all kinds of things and how
23 | they might be used and so on. So, this is a good step I
24 | think in terms of getting the information more widely
25 | distributed and making a point about the fact that we're

1 | interested in this area.

2 | One of the goals of our committee, at least, is
3 | that we need to facilitate this working relation between
4 | industry and academia and Food and Drug and so on.
5 | Clearly, this kind of thing I think does that. We're
6 | making that attempt to facilitate this kind of cooperation.

7 | Yes, Dr. Holt?

8 | DR. HOLT: We've used the word proprietary data
9 | here several times, and the difficulty is that our
10 | suspicion has been for some time that the really good data
11 | and particularly the kind of data that might answer the
12 | far-reaching questions that Frank has raised is probably in
13 | a domain in a company in many industrial settings that they
14 | don't readily want to share. The difficulty is, as I
15 | understand it at least, that when data comes to us it's by
16 | definition no longer proprietary. It might be new data,
17 | but because ours is a public forum, we have no way of
18 | participating in any kind of a confidential conversation.
19 | And that's fine.

20 | But I do suspect -- and we've talked about it
21 | before -- that if there was a mechanism by which we could
22 | sector a certain amount of our time, predescribed of what
23 | we intend to do and post-described what has and has not
24 | been accomplished, but still keeping the actual data set in
25 | confidence, that would help us.

1 Similarly, for these new things, the markers
2 that might come up after troponins have had their day in
3 the light, there's almost certainly a fair bit of that data
4 that the people who are generating this data would want to
5 keep the information in confidence at least for a time.
6 So, if there's a possibility of us getting that ability,
7 that capacity, that would I think greatly facilitate our
8 process. And my understanding is we can't do that right
9 now. Is that correct?

10 DR. DOULL: Well, that's what Helen said at our
11 last meeting. She implied that at least.

12 But we have expertise from Food and Drug, lots
13 of it. We have expertise from industry, lots of it. And
14 surely, this is a problem that has been wrestled with in
15 the past, and I guess what we need to figure out is -- we
16 don't need to rediscover the wheel -- if there's some
17 mechanism whereby we can address this problem and find some
18 kind of compromise that works, then I think we ought to
19 look into that. I don't know who would do that, Jim. Who
20 would we ask to help us get the expertise out there and how
21 to deal with proprietary information?

22 DR. MacGREGOR: Well, we have people in FDA
23 that deal with that that we would have to bring into it.

24 DR. DOULL: I think the point is if we
25 recognize it as a concern, then at least we can begin to

1 | explore who we can talk to maybe and find out if we have
2 | any approaches that would work.

3 | Jack?

4 | DR. REYNOLDS: It seems to me like this is an
5 | issue that may be overplayed a little bit. I think most
6 | anyone who would participate in this activity would
7 | certainly be aware there may be things of a proprietary
8 | nature that you would not want to divulge, but in my
9 | experience, they encompass mainly two areas. One is in the
10 | area of chemical structure, so you can keep that protected,
11 | and the other is not so much proprietary as that which
12 | would give you competitive advantage or you wouldn't want
13 | your competitors to know. And all of those things in my
14 | experience can be dealt with fairly easily. If you don't
15 | want to divulge competitive information, then you shouldn't
16 | participate in the experiments or this activity. And the
17 | other thing is, in terms of chemical matter, that's usually
18 | just a transient thing anyway until one has patent
19 | applications and things in place.

20 | So, I'm trying to think of an example where we
21 | have been bound by, if you will, this kind of activity
22 | based on the proprietary nature of the activity. It
23 | doesn't happen very often.

24 | Just one other thing, the main thing that
25 | companies want to do is when you divulge the information,

1 | the lawyers need to be aware of that so you can put in
2 | place when you should file patents. But most of us are not
3 | opposed to releasing a lot of this information.

4 | The last thing is in terms of data and data
5 | sets, when it comes to clinical information, most of this
6 | is protected by patient confidentiality and those kinds of
7 | things. But one can still anonymize or randomize the data
8 | and have access to this.

9 | So, my suggestion is we're maybe overplaying
10 | this a little bit, maybe trying to artificially constrain
11 | the activities of the group, because I haven't seen an
12 | example of where we've run into this yet.

13 | DR. DOULL: I think what we're saying, Ken, is
14 | that the chair has to, in a sense, be involved in this and
15 | aware of it and alert for potential problems, if they do
16 | exist. We'll explore the possibility of helping you by
17 | some kind of -- if there have been arrangements in the past
18 | that have been helpful in this or we can figure out some
19 | ways that would facilitate this.

20 | DR. WALLACE: I appreciate that. I especially
21 | am pleased that the NCSS is encouraging us to publish this
22 | data because that certainly was my desire.

23 | The way that I see that we'll develop this is
24 | we'll start with an outline, which is basically the slide
25 | that appears on page 3 of your bound copy. It's the

1 characteristics of an ideal biomarker. That will serve as
2 the outline for our document.

3 Then as we go through each of those
4 characteristics of an ideal biomarker, we will try to be
5 proving or disproving one of those arguments, and in the
6 process, we'll weigh the data that we have available to us
7 in the public literature. And if we come up shorthanded,
8 then at that point we'll have to stop and consider our
9 alternatives, and those alternatives would be to go to the
10 sponsor companies and ask for a sharing of data or to
11 design de novo new experiments to address those issues.
12 But as we make each of those individual arguments, we'll
13 reach that stage and see whether it's necessary or not to
14 approach the companies to share data.

15 Now, what we may want to include in this whole
16 thing is, once the whole document is ready, distribute it
17 to many of the sponsors, and as we make statements that the
18 data that we looked at, let's say, proved specificity, give
19 them the opportunity to react, if they want to share data
20 that's against whatever claims we make in that paper. We
21 could incorporate that into one of the near final stages of
22 our publication to make sure that we've looked at
23 everything.

24 DR. CAVAGNARO: Yes. I think that's a great
25 idea.

1 DR. DOULL: We talked at one of our meetings
2 about how you define a biomarker. Maybe that's going to
3 help us to get some good, acceptable definition of a
4 biomarker. It needs to be broad because this committee is
5 thinking biomarkers really broad.

6 DR. WALLACE: It's been helpful for the working
7 group to direct our discussions on that and limit them to
8 what are characteristics of a biomarker. Ironically, there
9 are several different subgroups not only within the agency,
10 but in other organizations as well, that have come up with
11 their definitions of what are the characteristics of an
12 ideal biomarker. And it would be nice to get us all
13 together because it doesn't matter what tissue, which drug,
14 whatever you're working on, the characteristics are the
15 same I would think.

16 DR. DOULL: Yes, that would be helpful.

17 Jack?

18 DR. DEAN: I want to support what Jack Reynolds
19 said, that I think that most of the companies, if you
20 anonymized the source of the information, the chemical
21 structure, and probably the indication, would have no
22 problem in providing some kind of bridging data, if they
23 have it. If it's in a clinical program, the data is
24 probably already with the FDA. So, as long as it's been
25 revealed to the agency in a good way, then I don't think

1 the companies would have a problem sharing the information.

2 The second point, though, Ken -- and I know
3 you're considering this -- is if this paper comes out being
4 sanctioned by some subcommittee of the FDA, that it has to
5 be of very high quality relative to the points that Frank
6 made and that I made earlier as well around sensitivity,
7 specificity, stability, transferability, et cetera because
8 everyone will follow whatever recommendations are made. I
9 would be concerned that we not just have one person's
10 experience, that we have multiple people's experience, and
11 the more you can pull information together from multiple
12 sources to validate whatever people believe, it would be
13 helpful.

14 DR. WALLACE: I would welcome the participation
15 of the NCSS in the review of this document. I agree with
16 you on that.

17 And, Dr. Reynolds, I would suggest that we
18 engage the NCSS early in the process, beginning with an
19 outline of the document to give you a chance to have some
20 feedback on that, and then as we develop the items in the
21 outline, at periodic stages again submit it to the NCSS for
22 review.

23 DR. DEAN: Really, I would also like to
24 encourage a presentation here by the working group of the
25 information because people may be willing to join in early

1 | in the process of helping provide additional information if
2 | it's needed. It may not be needed.

3 | DR. REYNOLDS: I missed the presentation at ACT
4 | and some of the background to that, but what I hear you
5 | telling us today is that you have found the biomarker for
6 | cardiotoxicity and that your work now, as I understand it,
7 | is being wound up in terms of defining the troponins.
8 | That's how I understood that. What activities do you have
9 | to look at other measures of cardiotoxicity or to ensure
10 | that troponins are in all cases the biomarker that we would
11 | want for cardiotoxicity?

12 | I guess what I'm saying is we're here to try to
13 | determine how we can help your group move things forward,
14 | and it sounds to me like what you're saying is that what
15 | you needed us to do is to review your paper and not to
16 | stimulate further research or further activities. I know
17 | I'm probably missing something.

18 | DR. WALLACE: No. This is the first in a long
19 | process. I want to be very careful that the committee
20 | believes that the troponins mark myocardial cell injury,
21 | but that's not the only type of drug-induced cardiac injury
22 | that occurs. So, we're suggesting that the troponins will
23 | be used to flag that type of injury and perhaps even to
24 | measure it in terms of a dose response.

25 | However, we have not yet addressed issues of

1 | what kind of cardiac injury occurs that troponins do not
2 | mark and what are other markers then that we can use to
3 | cover those types of injuries as well. So, this is just
4 | the first stage of a much longer process we believe.

5 | DR. DOULL: Back some time ago when this
6 | subcommittee was looking at this, we looked at a bunch of
7 | biomarkers, and it appeared to us that the troponins were
8 | kind of out ahead, that they had more data behind them and
9 | so on. So, that was a logical first group to focus on.
10 | And I heard you say, Ken, that part of the group at least
11 | will be looking at other biomarkers and evaluating those,
12 | and that's part of the evaluation of troponin as, in fact,
13 | a biomarker, is that comparison with other biomarkers.
14 | Down the road, I would imagine you all or another committee
15 | would be looking at other biomarkers of cardiac toxicity
16 | someplace.

17 | DR. WALLACE: And we'll start that process at a
18 | much lower level where we'll need a lot more data
19 | generation in the early stages of those discussions than we
20 | had to have for troponin. Much of that data was already
21 | out there.

22 | DR. CAVAGNARO: I think John had discussed it
23 | and others. The whole focus is to identify these markers
24 | to support clinical decision making, and so when you
25 | validate the marker, it's to a functional endpoint, to a

1 histopathology. You had talked about some microscopic
2 changes, whether or not they were there. Or really to a
3 clinical finding.

4 So, the database really needs to have a
5 significant number of cases where you see cardiac toxicity
6 -- I mean, to me cardiac toxicity in humans -- and have
7 missed it in the animal studies by the standard methods
8 because again, we're not trying to assess cardiac toxicity
9 in the animals. We are trying to introduce a new biomarker
10 to help us predict clinical toxicity. But I'm sure that
11 that's all part of the --

12 DR. DOULL: I think Jack raises another point,
13 and that is in the sense that you guys are a working group
14 of a subcommittee of a Food and Drug advisory committee,
15 your reports and statements and what have you carry some
16 weight which have to do with later on when a company comes
17 to get cardiovascular drugs approved and so on, it may have
18 some influence. I guess we need to think about that
19 because that raises a potential problem I guess in the
20 sense that because you are a working group of a Food and
21 Drug subcommittee and all, what does that imply. I guess
22 we're probably going to need some help, Jim, to be sure we
23 do things correctly in developing all this and moving it
24 along.

25 DR. WALLACE: That's why I was slow to answer

1 | your question about publishing because I didn't know if we
2 | had -- but I agree.

3 | DR. SISTARE: I want to come back to something
4 | that Joy mentioned. I think we have to be clear that what
5 | we're asking the expert working group to do is to provide
6 | data that indicates that troponins are excellent reporters
7 | of myocardial damage. Now, they can do that in the animal
8 | study because you can take the heart and you can look at
9 | it, and you can ascertain that the damage is actually
10 | there.

11 | Joy is asking a more complex question, and that
12 | is whether the animal model is predictive of the clinical
13 | manifestation of cardiac toxicity. That's a more complex
14 | question that's going to take a lot more work. The
15 | troponins could probably be the bridging tool to answer
16 | that question if they were measured in each and every
17 | study. But the amount of experience I believe with
18 | troponins in the clinic not to measure myocardial
19 | infarction but to measure drug-induced myocardial injury is
20 | pretty small. There's a good history for certain clinics
21 | using it to monitor the onset of doxorubicin myocardial
22 | damage.

23 | I forget the substitute speaker that spoke, but
24 | anyway, we challenged him with that question. He mentioned
25 | a few cases. I think tributylene infusions were given in

1 the clinic and they looked at troponins and they didn't see
2 increases. Another case. I forget the drug that was given
3 for infants for patent ductus arteriosus, and they did not
4 see again that there was an increase in troponins.

5 But it hasn't been rigorously assessed.
6 Studies like asthmatic patients taking puffs of
7 bronchodilators and what happens to troponins in those
8 cases haven't been done. And those are going to be
9 important I think to get it incorporated into the clinic.
10 But I think we have to do it one step at a time here and
11 focus on the nonclinical benefits we can get out of this
12 with the hope that this biomarker can serve as a bridge to
13 move into clinicals. But I don't know that we're there
14 just yet. Let's take it one step at a time.

15 DR. DOULL: Yes, Jim?

16 DR. MacGREGOR: My understanding of the focus
17 of the topics chosen by this group is that particular
18 attention should be paid to the accessibility of the
19 markers that were considered by the groups for the express
20 purpose that they could serve this purpose as a bridging
21 biomarker. My understanding is not in the sense that the
22 animal model would predict the human, but rather in the
23 sense that the marker chosen could measure the same class
24 of damage in the animal and the human so that you could
25 then relate the animal data to the clinical situation and

1 have a bridging marker that let you study similar processes
2 in both species. That's my understanding of the charge.
3 And I would encourage the working group to strongly
4 consider that aspect, the extent to which the markers under
5 consideration can serve this bridging function.

6 DR. CAVAGNARO: Can I ask a question? So, if
7 the FDA were to somehow down the line recommend to sponsors
8 to include troponin as a marker in preclinical, I guess to
9 me I'm a bit confused, that then the clinicians wouldn't
10 ask for that same marker in the design of the clinical
11 program if there was a signal in the preclinical. So, I
12 guess now I'm totally confused about the bridging biomarker
13 because I thought what we were looking at is measurements
14 that we could look at in preclinical and clinical.

15 DR. MacGREGOR: Absolutely, yes. I guess what
16 I was commenting on was I thought Frank indicated that the
17 animal model should be predictive, which it always has to
18 be predictive, of course, but it kind of mixes two
19 concepts. Do you have the right animal model for the human
20 is one concept, but do you have a marker with which you can
21 measure particular type of damage in the animal or in the
22 human is a slightly different concept. And I think it's
23 the second concept that we're --

24 DR. CAVAGNARO: Right. So, we're clear. So,
25 if we were to recommend troponin in preclinical studies,

1 | then the clinicians on the team would recommend it in their
2 | clinical program. Is that true?

3 | DR. PAPOIAN: Not necessarily. One way to
4 | think about troponins is like we would do for liver
5 | toxicity testing. If there was evidence of liver toxicity
6 | in the animals and say you had elevations of the
7 | transaminases, coupled with histopathology changes, we
8 | would make the same recommendations to the medical officers
9 | for their clinical trials and that they would add those
10 | markers to the clinical trials for testing not as a
11 | routine, but just as a screen, as a biomarker in those
12 | cases where there are signals in animals to monitor
13 | patients appropriately for those same sort of toxicities.

14 | DR. CAVAGNARO: I think we're saying the same
15 | thing.

16 | DR. PAPOIAN: I wasn't sure if that was the
17 | case. It sounded like you were maybe asking if we're going
18 | to routinely ask for troponins, are we going to routinely
19 | ask for troponins in clinical trials. That's what I
20 | thought you said.

21 | DR. DOULL: Yes. But the reason for asking for
22 | asking for them in the animal studies is because we hope
23 | they will have some predictive significance in the clinical
24 | trial.

25 | DR. PAPOIAN: Correct, yes.

1 DR. DOULL: There are studies that I guess that
2 we do in animals for which there is no clinical
3 significance like the NTP studies on carcinogenesis. Who
4 knows? But sometimes they do, sometimes they don't.
5 That's one of the questions that the working group has to
6 look at, is this just a test that's just valuable in
7 animals to detect cardiac damage or is it in fact
8 predictive for something further on. That's something that
9 you guys have to deal with in a sense.

10 DR. WALLACE: If I could comment on Frank's
11 statement about the paucity of that data that's out there,
12 that might be the type of data where we could actually mine
13 it from some of the sponsor companies. They may have that
14 data from their clinical trials that isn't necessarily
15 available in the public literature that we might be able to
16 get at. I'm an optimist.

17 DR. DOULL: Jack.

18 DR. DEAN: Just to clarify what Joy was saying,
19 the way I interpreted what you were saying, Joy, is you
20 thought if this was a great marker, we ought to routinely
21 include it in preclinical. And I would caution us about
22 wanting to do that yet.

23 We just had a research meeting last week where
24 we looked at what's happening in discovery and in
25 pharmacology, and within our company and I suspect most

1 | companies, this marker is being used to study reperfusion
2 | injury and protecting against ischemic injury. And it's a
3 | very impressive marker in the animal models in that sense.

4 | I think that if we then went on to look at this
5 | particular compound in development in the clinic, we would
6 | want to carry that marker into the clinic to look at
7 | protection against injury. But I would not think that we
8 | are at a point of wanting to routinely include it. Maybe I
9 | misheard what you said.

10 | DR. CAVAGNARO: Yes, you did. But the latter
11 | half was right. If you said it was worthwhile in the
12 | animal studies, then I think there's no other choice but to
13 | continue it on in the clinic. So, the last half is right.

14 | But, no, I'm not making a recommendation for
15 | routine use in screening. That was one of my first
16 | questions. Are we talking about screening versus
17 | mechanistic here? And it sounds like more the latter if
18 | you have a signal that you're concerned about. Although I
19 | appreciate your concern of the unknown with a new class of
20 | agent where you present it, but again, I think I'm, at
21 | least at this stage, more toward the latter, more the
22 | mechanistic part of it.

23 | DR. DOULL: Our goal is not to prevent heart
24 | damage in rats. We're concerned about more than that.

25 | Other questions? Yes, Dr. Holt.

1 DR. HOLT: To emphasize something that came up
2 in the conference, the assays themselves have some
3 challenges. We heard about some differences that have been
4 observed between different assay platforms. I just want to
5 caution a little bit of slowdown here, that this is part of
6 what will need to be documented inasmuch as we can document
7 it. There are some challenges with the assays, but we feel
8 pretty bullish about troponin itself. I'm sure everybody
9 will be relieved to hear this, that it will be a while
10 before I think anybody can put their hand on their heart
11 and recommend all animals and all humans --

12 DR. CAVAGNARO: So, is it you have to take a
13 separate blood draw? Is there something special about it?
14 You could just include it as one of the standard SMAC
15 analyses?

16 DR. WALLACE: It's fairly noninvasive. Just a
17 small, like 200 microliters of blood or whatever is all
18 that's needed.

19 The problem that Dr. Holt is referring to is
20 that there's not a good standardization of the assay
21 itself. It's an antibody-based assay, and there's a lot of
22 variability between the individual assays. So, a number
23 generated in one lab may mean nothing to a different number
24 generated in another lab. So, we have the issue of
25 standardization of the assay itself.

1 DR. SISTARE: But I would hasten to add that
2 there is one assay for troponin T and there are about -- I
3 don't know -- 24 or something like that for troponin I.
4 But all of those are approved by FDA's Center for Devices.
5 So, they have approved each of those assays with the caveat
6 that here is the limits of each of the assays. Here's what
7 you can detect, here's the linear ranges, these kinds of
8 things. So, each one has their own performance
9 characteristics as Ken has mentioned, and they're all over
10 the map.

11 DR. DOULL: Well, I'm taking a couple of things
12 away, Ken, that you have brought to us to look into, and
13 one has to do with what it means when a working group, for
14 example, makes recommendations and presents data and so on.
15 We'll look into that. Also, the business about -- it's
16 similar to the publication issue, whether we have any
17 concerns about how we do that and what all that means.

18 I think the other thing that I would say is
19 that this subcommittee is very anxious to facilitate the
20 work of your group. So, we're going to try to help you in
21 any way that we can, and I think that means, as you've
22 said, we need to talk to each other frequently and see to
23 it that we have good communication between this group and
24 your group.

25 DR. WALLACE: I appreciate that. I think the

1 whole process of developing the publication is going to
2 challenge us to further define the relationship between the
3 two groups because it's very likely we'll be coming back to
4 the NCSS in the publication process saying that we need
5 access to data. Will you help us gain that access to the
6 proprietary data? So, we'll engage at that point.

7 We also may come back to the NCSS and say we
8 need to conduct additional experiments. One of our
9 activities is designing this experiment. Once it's
10 designed, we'll then have to say, well, who is going to do
11 it and who is going to pay for it and how is it going to be
12 done. So, we'll be coming back to the NCSS for guidance on
13 that as well.

14 DR. DOULL: I'm pleased that money is the last
15 thing to come up. We've gone through all the science and
16 now we're willing to talk about budgets.

17 DR. CAVAGNARO: Just back to the publication
18 because I think that that is key for the data to be out
19 there. This advisory committee is a bit different because,
20 in general, advisory committees can make recommendations
21 and the agency can decide to accept them or reject them or
22 some variation. So, that would be easy. But this advisory
23 committee has FDA representation on it. Oh, it doesn't?
24 Are you members?

25 DR. MacGREGOR: Not the advisory committee. A

1 formal recommendation to FDA eventually would come from the
2 full advisory committee.

3 DR. DOULL: From the advisory to the
4 pharmaceutical. We are a subcommittee.

5 DR. CAVAGNARO: So, then that committee doesn't
6 have FDA representation on it.

7 DR. DOULL: We would make a recommendation to
8 that committee, and then they would make the recommendation
9 to the agency.

10 DR. CAVAGNARO: And that committee doesn't have
11 any --

12 DR. DOULL: Helen, you got here just in time.

13 DR. CAVAGNARO: Okay, so that makes it a little
14 bit easier.

15 Can you just comment about this process and the
16 ICCVAM process? The rationale behind ICCVAM is to
17 introduce alternative methods across interagency type. So,
18 how do you see this initiative and the ICCVAM initiative?

19 MS. WINKLE: Well, certainly the main reason
20 for setting up this subcommittee to the advisory committee
21 was to get input on a variety of different projects that we
22 might work on as far as ensuring that we could meet the
23 scientific need and go through the advisory committee to
24 get credentialing basically of those projects and
25 acceptability of those projects throughout all FDA.

1 I think that differs a little bit from the
2 purpose of ICCVAM. Now, Jim may have more comments on this
3 and understand a little bit more the difference between
4 ICCVAM and how the advisory committee works. But I see
5 this as on a whole different level.

6 Some of what we had hoped to be able to do was
7 to help with the funding of the projects through this
8 process with the support of the agency. So, that was
9 basically our thoughts in setting up this subcommittee.

10 DR. DOULL: Jim?

11 DR. MacGREGOR: Actually I was thinking I might
12 bring this issue up later in the more general discussion
13 that was scheduled for the subcommittee because it's really
14 kind of the next stage. If this expert group, for example,
15 finds that it would be valuable to use troponin in certain
16 circumstances and defines that, then it will come to the
17 committee to make a recommendation of some sort, and that
18 could take a number of forms. This is something the
19 committee will need to think about in the context of
20 whatever the findings are when all the data comes together.

21 But basically I see two mechanisms in place.
22 One is the committee could make a recommendation to FDA
23 that a particular assay ought to be used and maybe there
24 ought to be an FDA guidance on this topic. So, that could
25 be a typical kind of recommendation that could go from an

1 | advisory committee to FDA to consider.

2 | But another thing that I just thought I might
3 | put on the table for some thought is that actually ICCVAM
4 | is undergoing a redefinition of itself at the moment, for
5 | those of you who are following what's going on in ICCVAM.
6 | It was reauthorized last year, and as part of that
7 | reauthorization, it's actually rewriting its own operating
8 | rules and structure and so on. A major part of the ICCVAM
9 | function for FDA -- it's 15 different agencies, 14 plus
10 | FDA, involved in ICCVAM are thinking about this, how is it
11 | operated, how should it operate.

12 | So, if this committee were to feel that if
13 | ICCVAM were to restructure in a certain way to consider
14 | broader recommendations for biomarkers or whatever, this
15 | would be an opportune time to think about that. It's a
16 | good time to begin to think about it, but what is
17 | recommended probably will depend on the findings of the
18 | expert groups.

19 | DR. DOULL: We should put that on our agenda,
20 | Jim, and probably have somebody from ICCVAM come talk to
21 | us.

22 | Helen Winkle, for any of you who don't know
23 | her, is here.

24 | A couple of things that came out of the
25 | discussion so far had to do with proprietary data, that the

1 | committee may want to look at proprietary data. The
2 | publication. Does the committee publish on their own or
3 | does it have the mantra of the Food and Drug on the
4 | publication, and what does that mean in terms of
5 | responsibility of the agency toward those activities?
6 | Those are general concerns that will affect -- well, and
7 | finally, I guess the budget things. Those are things that
8 | will affect both working groups I'm sure. So, those are
9 | things you might want to address.

10 | MS. WINKLE: Well, it would be nice if I could.

11 | (Laughter.)

12 | MS. WINKLE: I think definitely these are
13 | issues that we need to look at in general as far as this
14 | subcommittee is concerned, but we'll have the same question
15 | come up with other subcommittees under the advisory
16 | committee. I think we're feeling our way with this
17 | subcommittee. I think as far as proprietary data,
18 | publications, et cetera, we need to put some information
19 | together and be able to address these issues, and I'm not
20 | ready to address them right now. Some of them are just
21 | coming up for the first time here. So, I think they're
22 | definitely very good issues. What I probably need to do is
23 | go back, have some conversation with some of the people in
24 | various organizations, and maybe we need to bring someone
25 | in here to answer those questions at the next meeting. But

1 let's try and capture all of those.

2 DR. DOULL: And we will, Ken. That's what
3 we're here for.

4 Are there any other questions or messages that
5 we have for our working group on cardiotoxicity? Yes,
6 Jack.

7 DR. REYNOLDS: Yes. I was taken by the
8 definition you provided for a biomarker. I don't know if
9 that was something your committee came up with
10 independently or not, but I think that is probably the gold
11 standard by which other biomarkers would be compared. To
12 me it was the most comprehensive definition I've seen. Not
13 that all biomarkers would do that, but certainly as we look
14 at product profiles, we certainly know what we're shooting
15 for and we know when we haven't made it according to your
16 definition. But I would just like to commend you. If that
17 is in fact some original work from your committee, it in
18 fact is a very good definition. I think it's very workable
19 for those people in the area.

20 DR. DOULL: That's that characteristics of the
21 ideal biomarker.

22 DR. WALLACE: Thank you. That has been a focus
23 of a lot of the committee discussions and we've used it as
24 a guiding principle in our discussions. I venture to say
25 that that's not the latest version of it, but we hopefully

1 | have improved it one more edition. But thank you.

2 | DR. DOULL: We'll massage that a little. It
3 | looks like a good definition for us. We'll have a whack at
4 | it too. Why not? Right, Joy?

5 | Thanks, Ken.

6 | Then we're going to hear about the vasculitis,
7 | and Tom, you're going to do the vasculitis presentation.

8 | DR. PAPOIAN: You may or may not know the co-
9 | chairs, Bill Kerns and Lester Schwartz, were unable to
10 | attend because they're contributing to the financial
11 | difficulties of the airline industry.

12 | So, as I go through each slide -- and this is
13 | the first time I've actually seen them. I didn't see these
14 | before this morning, but I've been part of all the
15 | discussions of the working group up until now.

16 | And if anybody wants to make any comments
17 | during the course of this presentation, then feel free to
18 | do so.

19 | Just a quick thing. I just wanted to make a
20 | comment about what Jack just mentioned about the gold
21 | standard for biomarkers. It fits, in my opinion, perfectly
22 | for troponins, but whether it will be appropriate for
23 | markers of vascular injury is another story. And that's
24 | where it will be a little more difficult to fit those sort
25 | of high standards.

1 In the first slide, we've had a couple telecons
2 in the last several months, and just last week at the
3 American College of Toxicology, we had several hours of
4 presentations by the various members of the working group
5 on their individual research projects.

6 One of the other things part of this working
7 group has been trying to do is identify terminology.
8 Originally we had gone into the working group called the
9 Vasculitis Expert Working Group, and this became an issue
10 mostly for the reasons that from a clinician's point of
11 view, vasculitis is thought to be an immune-mediated
12 disease, and here we're talking about non-immune-mediated
13 drug-induced vascular injury in animals as essentially the
14 lesion that prompts regulatory concern.

15 One of the other aspects of finding biomarkers
16 for vascular injury or vasculitis is that there aren't any
17 available. And this is what the real difficulty is. If
18 findings are found in animals, how do we monitor for such
19 effects in humans? On the slide, it says, complete absence
20 of biomarker leads. There are probably long lists of
21 clinical inflammatory biomarkers that are currently being
22 utilized and examined and researched for monitoring markers
23 of vascular inflammation as risk factors for
24 atherosclerosis, but essentially there's no validated
25 biomarker that can sort of tie together animal and human

1 studies.

2 One of the issues that the Vascular Injury
3 Working Group has been trying to deal with is focusing
4 exactly what the next steps are going to be and how to
5 obtain a certain finding for various projects, particularly
6 for the academic members of the group who are
7 representative from academic situations.

8 And then also the intellectual property rights
9 is also something that this working group has also been
10 trying to deal with. Are there certain drugs that still
11 have patents or are owned by drug companies? If they do
12 research on these drugs, how is that going to be reported
13 and how is that going to be dealt with and be able to keep
14 your proprietary information?

15 Future plans is what I guess is going to happen
16 after this group in subsequent meetings. Some of those
17 issues I just mentioned will be part of the future plans.

18 Terminology. As I mentioned before, the issue
19 of vasculitis versus vascular injury, rather than having it
20 discussed at the whole group, essentially Robert Johnson
21 and myself have had several discussions regarding which
22 would be the more appropriate terminology. When it comes
23 to identifying a biomarker, one of the issues of focusing
24 on the inflammatory component is that you don't necessarily
25 incorporate the initial lesions of the endothelial cells,

1 | smoothe muscle cells, subsequent possible repair processes
2 | that occur afterward, even though vascular injury would
3 | entail and would encompass the inflammatory component as
4 | well. So, whether we're talking about vasculitis or
5 | whether we're talking about vascular injury as an
6 | initiating event with all subsequent processes that occur
7 | after that injury as a potential source of finding one of
8 | more biomarkers was the reason for trying to essentially
9 | redirect the terminology into a more encompassing term such
10 | as vascular injury.

11 | The clinical and preclinical observations have
12 | to do with the fact that vascular injury or drug-induced
13 | vascular inflammation is well described in many drugs that
14 | are submitted to the agency. One of the difficulties is
15 | finding evidence of drug-induced vascular inflammation in
16 | humans, and the only time it has been looked at is in the
17 | case of minoxidil. In those cases, they looked at autopsy
18 | specimens from minoxidil-treated patients and found no
19 | obvious drug-induced lesions.

20 | One of the other problems with trying to find
21 | sequelae of vascular injury is how would one monitor for
22 | subsequent events. And one of the possible clinical
23 | subsequent events would be rupture of vulnerable plaques
24 | and that would occur because we have vascular inflammation
25 | and trying to pick up such a signal such as myocardial

1 | infarction may not be necessarily an easy thing to do in
2 | small-scale clinical trials. It may require some sort of
3 | large-scale monitoring after a drug is on the market or
4 | some sort of clinical trials that are done after a drug is
5 | outside.

6 | As far as how to influence the selection of
7 | potential biomarkers, that again is simply what I just
8 | described. If we're looking at the injuring event, as well
9 | as the repair and all the inflammatory processes that occur
10 | in between, that's the range that the subcommittee is
11 | trying to focus -- is really not focusing but leaving the
12 | arena wide open as far as what potential biomarker will
13 | eventually be correlated with these drug-induced changes.

14 | As I mentioned, the subgroup was established
15 | between myself and Bob Johnson to look at the terminology.
16 | One of the things that we will try to do is develop a
17 | glossary of terminology, something that we discuss all the
18 | various terms to make sure that we all understand and have
19 | the same understanding and definitions of the terminology
20 | that we're trying to encompass, including the biomarkers
21 | themselves, as well as the lesions and the cells that are
22 | involved.

23 | These will be put into a draft, it looks like,
24 | by next March, and so we'll get that together.

25 | The working group also wanted to get a copy,

1 when it's available, of an internal draft guidance on drug-
2 induced vasculitis that the Center for Drugs and Center for
3 Biologics are currently working on. Once this gets
4 published in the Federal Register, then the working group
5 would like to have some comments and review that as well to
6 make sure that we're all on the same page on that.

7 Just real briefly, the draft guidance takes a
8 risk assessment approach to findings of drug-induced
9 vasculitis in animals.

10 The research budget. Now, I can't address this
11 too much myself, and if there are any comments on here, I
12 would be happy to hear any comments.

13 The ILSI update. I believe that we're
14 discussing aspects of how to obtain funding. ILSI
15 apparently may be a potential source for that, as well as
16 standardization of protocols and getting sort of a
17 consortium of methodologies together.

18 There were apparently some discussions with
19 NCTR to see if there's any way that research programs can
20 be funded. I'll defer these points maybe to the
21 discussion.

22 There was a plan to look to NTP, as well as
23 contacting NIEHS, for potential ways that a particular
24 project can be funded.

25 Also, Pharma apparently is another source that

1 I believe was contacted following our last meeting last
2 week to see if there's any way that they can help
3 collaborate in this endeavor, and also Pharma and NCTR may
4 be good sources where this working group feels that that
5 might be promising.

6 Now, as far as the targets themselves, the
7 working group, as I mentioned, is really leaving nothing
8 out. It's looking from the very initial phases of injury
9 to the first changes that we see at the endothelial cell
10 layer. There's evidence of possible apoptosis occurring.
11 Some of the endothelial cells apparently detach and
12 circulate. The following inflammatory component, of
13 course, has its cytokines and acute phase proteins that are
14 possibly elevated. There may be a repair phase. Markers
15 there are worth looking into.

16 And regarding whether it's a fishing expedition
17 or not, it is focused in the sense that it is looking at
18 vascular injury, but since there are so many potential
19 candidates in cells in up-regulations of surface membrane
20 proteins, as well as released cytoplasmic constituents, as
21 well as changes in gene expression in the involved cells
22 themselves, not just the target vascular cells, but also
23 the inflammatory cells themselves, are all potential
24 targets. In a way, it may be a fishing expedition, but we
25 have a pretty good idea of what cells and what methodology

1 is available to us.

2 A recent interesting approach was using NMR
3 spectra to look at urinary proteins or urinary
4 constituents. In fact, they're not proteins, but
5 everything except proteins, as well as possibly in plasma.
6 This is very sensitive methodology that needs to be really
7 validated to make sure how well it correlates with actual
8 injury.

9 And then proteomics is also being currently
10 examined as well.

11 As I mentioned, the urinary NMR markers seem to
12 be very interesting. They're very sensitive. Specificity
13 is an issue that still remains to be established. It does
14 require a lot of validation, and that's something that I
15 think both subcommittees are working on.

16 There were some early results with PDE,
17 phosphodiesterase, IV inhibitors as a potential research
18 tool to see how to correlate the actual lesions themselves
19 with the actual changes that one can monitor either in
20 blood or in urine.

21 The acute phase proteins were shown to be
22 changed with some of these compounds with the PDE III
23 inhibitors particularly in the various species, and how
24 this correlates with changes in acute phase proteins in
25 humans still needs to be established.

1 And the concept of circulating endothelial
2 cells as a marker of vascular damage is something also
3 that's being looked at. Here again, too, whether these
4 sort of assays and markers hold the criteria of a gold
5 standard for a biomarker is probably a little more
6 problematic, and I'm speaking here my own opinion that
7 because these sort of changes can occur in all sorts of
8 conditions either naturally induced, infectious, or drug-
9 induced, and so these sorts of things have to be correlated
10 with drug exposure specifically. That's where these will
11 have to be key.

12 And the next steps. As far as the committee
13 members go, several of the people are still involved in
14 their own independent research either with their own
15 pharmaceutical companies or in their own independent
16 academic labs.

17 We also need to work in parallel to see if we
18 can get a standard model for testing. In other words, we
19 want to examine all the species, but a lot of the data,
20 particularly when it comes to assays for these particular
21 constituents, is usually human-specific or mouse-specific,
22 and we need to get more data in the standard species that
23 are used in studies for support of drug submissions. Those
24 are rats and dogs, mini-pigs and primates.

25 We need to select a few compounds, and I think

1 | the list can be longer than shorter. I think there's no
2 | lack of potential compounds that are known to induce these
3 | lesions in animals. Also identify who is going to supply
4 | these compounds. Some you can buy off the shelf. Some are
5 | still proprietary. Where is that money going to come from
6 | if it needs to be purchased?

7 | We need to develop a standard protocol for, I
8 | guess, looking at different species to be able to correlate
9 | specifically whether rats and dogs and humans share the
10 | same endpoints and effects to the same drug, and also agree
11 | on those endpoints.

12 | We need to establish some sort of centralized
13 | way of doing these animal studies, and I'm not sure about
14 | this one so much as far as understanding that other than if
15 | there's going to be a central source for the animals,
16 | somebody is going to actually do the dosing and the
17 | analysis for the group or for several people involved.

18 | Also, consider asking other people to
19 | participate in these studies, that we haven't done so
20 | already, and there are probably lots and lots of people out
21 | there that might have interest in this. Particularly, I
22 | think there's possible other academic labs that, if there
23 | was a source of funding, either through NIH or other
24 | sources, they might be willing to do some studies in their
25 | own laboratories.

1 And the goals. Again, to look at biomarkers
2 that give you an idea of the mechanism, because one of the
3 things that was discussed in the committee is rather than
4 identifying a specific protein or marker that's elevated in
5 an animal and looking for that specific marker in humans,
6 also another way to think about it is to look at the
7 mechanism that was affected and look for a similar
8 mechanism marker in the humans.

9 And also look at late-stage biomarkers. That
10 way you'd be able to find biomarkers -- you don't have to
11 monitor people like right way after they take a drug, but
12 hopefully the next time they come in for their clinical
13 visit, a week or so later. That certainly would have an
14 advantage.

15 And also, use all the technology that's
16 available to us today of genomics, proteomics, and
17 metabonomics.

18 And finally, the time line as far as when this
19 is all going to be accomplished. I guess we're looking at
20 February of next year to having an agreement on the study
21 protocols and the appropriate endpoints to proceed on.
22 What are the good model compounds that we need to use and
23 just start using selected models so we can share data
24 on using the same methodology in the same compounds,
25 and somehow agree on the collaborative responsibilities,

1 | who's going to do what and how is this all going to fit
2 | together.

3 | Finally, as I mentioned, the terminology
4 | position document would essentially just make sure that
5 | whatever we call vasculitis, we all agree on what we mean
6 | by that or any other terms that we throw around.

7 | Define a budget for purchasing particular
8 | compounds that we need to test and be able to review all
9 | the data that comes in from the committee. And finally,
10 | finalize the plans between NCTR, the pharmaceutical
11 | industry, and Pharma and any other support that we can
12 | possibly generate.

13 | Further on the time line, from next April to
14 | the following March, actually start possibly some of these
15 | protocols, actually start the studies themselves, after we
16 | have consensus on the protocols and the drugs that we're
17 | going to use, and then somehow have a central place to
18 | compile all the data.

19 | Then in March of 2003, review the first data
20 | sets from these experiments and finalize plans I guess for
21 | a time line for guidance recommendations if that's
22 | appropriate as an end result being a guidance.

23 | Then November of 2003, have a target date for
24 | an initial biomarker. That would certainly be optimistic
25 | to have such a thing by that time, given the complexity of

1 | the various issues involved, but that would certainly be a
2 | reasonable thing to begin with.

3 | And finally, the committee members: Bill
4 | Kerns, Les Schwartz, David Essayan, Don Robertson, Fred
5 | Miller, Kerry Blanchard, Jim MacGregor, Frank Sistare, Paul
6 | Snyder, Prakash Nagarkatti, Robert Johnson, Scott Burchiel,
7 | and myself.

8 | Thank you. I guess we will open it up for
9 | discussion.

10 | DR. DOULL: Jim.

11 | DR. MacGREGOR: Just a point to keep the record
12 | straight. The way we've set up these committees, we
13 | actually had an FDA process with representatives across
14 | centers to select the experts in these areas, and then in
15 | addition, we assigned center liaisons to the committees.
16 | So, some of the people on these slides listed as committee
17 | members, in fact, are the FDA center liaisons to the
18 | committees. We have actually only one FDA member who is a
19 | formal committee member, and that's Gene Herman on the
20 | cardiac injury group.

21 | DR. DOULL: It is clear that this report and
22 | the previous report are quite different. In the previous
23 | report, you guys have kind of focused in on troponins, and
24 | in this one you're really surveying the field to find out
25 | which one is really going to be the best.

1 I think this is a very exciting, a very
2 fascinating kind of program and one that would, in fact,
3 move us ahead to do exactly what it is you're intending to
4 do.

5 You talk about focusing on injury and on
6 repair, and I guess I'm thinking about the time line for
7 that. Frequently the time line for injury is rapid and the
8 time line for repair is very slow, and I'm wondering if
9 looking at the time of that will help in designing those
10 studies.

11 The other thing, ILSI has just finished a big
12 cooperative study on cancer. I don't know how they did
13 that, Jack. They went to industry and got support to do
14 all those tests of all the various carcinogenesis testing
15 procedures, and then the companies tested each of those
16 against selected --

17 DR. DEAN: You're referring to the genomics
18 program?

19 DR. DOULL: Right, and Ray Tennant's animals
20 and so on.

21 What you're talking about sounds kind of
22 similar to that, that there would be a list of drugs or
23 agents that would be useful in this procedure. You would
24 look at it against a variety of biomarkers, and out of that
25 hopefully would come some clues as to direction. I gather

1 | that is sort of what your committee is thinking about.

2 | DR. PAPOIAN: Yes, that's right. The list of
3 | compounds I think is one of the first things. Actually
4 | they sort of working independently to first identify the
5 | list of potential biomarkers that one can use, that assays
6 | are available. If no assays are available, how do we go
7 | about developing certain assays to be able to detect them
8 | in very small amounts most likely. And then to validate
9 | the actual markers themselves, we need to have a standard
10 | or small list of compounds to use.

11 | Now, there's no shortage of experience as far
12 | as what compounds cause lesions in animals. I think one of
13 | the issues was which ones are proprietary. How do we
14 | obtain the ones that are not proprietary? Where is the
15 | funding going to come from? Which ones are we going to
16 | buy? But we can certainly select anywhere from a half a
17 | dozen or less. That's not a problem. And to be able to
18 | agree on these are the ones we're all going to test and use
19 | as the validation compounds. That's the thought currently
20 | right now.

21 | DR. DOULL: Let me ask one other thing. You're
22 | mentioning the Food and Drug paper. That will help, you're
23 | saying, because it will talk about some of the same areas
24 | and so on?

25 | DR. PAPOIAN: I'm not sure how much it will

1 help because it's a guidance to be used for reviewers, as
2 well as for industry, for everyone to be on the same page
3 as far as when findings of vasculitis are shown to occur in
4 animals, how appropriate risk assessment is done to
5 determine what the human risk is in those cases. The
6 guidance right now is in a draft stage. The subcommittee
7 members have had their input, and it's just a matter of
8 putting it into the correct format for inclusion in the
9 Federal Register at the stage it is now.

10 But the process essentially -- there are a
11 couple members here at this table -- is using standard
12 assessments of safety margins, therapeutic indexes,
13 mechanisms, known mechanisms, whether these are species-
14 specific effects, whether they occur only in dogs, whether
15 they can possibly extrapolate to humans. But those are all
16 considerations as far as how we determine whether a
17 compound has potential human risk.

18 DR. DOULL: That paper focuses on vasculitis.

19 DR. PAPOIAN: That's correct.

20 DR. DOULL: Whereas, you guys are looking
21 broader at vascular injury.

22 DR. PAPOIAN: We're looking for ways to monitor
23 these effects in humans. We're trying to find a biomarker
24 for if these effects occur in humans. The only tools we
25 have now are just standard risk assessment tools. Having

1 an appropriate biomarker for monitoring patients is the
2 task apparently of the working group, to be able to have
3 some tool to allow these drugs to continue in clinical
4 development, the safeguard being that you can detect these
5 lesions if they were to occur in humans.

6 DR. DOULL: Questions for the Vascular Injury
7 Group? Yes, Jack.

8 DR. REYNOLDS: Yes. I think Tom has focused on
9 several points that I would want to make.

10 One, I think we talk about biomarkers, and I
11 think when you look at cardiac toxicity, you can begin to
12 imagine a biomarker like a troponin. I think with
13 vasculitis, because there are multiple components of the
14 organ, if you will, that are involved, there are multiple
15 pathogenesis to the injury and the repair and the like, I
16 think to target for a biomarker at this point in your
17 research activities to me is kind of narrowing the field.
18 I guess the term I use and would propose is helpful is if
19 there were a diagnostic that would help us identify
20 vascular injury from that diagnostic, where we identify
21 that, we might be able to go back and identify a biomarker.

22 I think that certainly in my experience with my
23 own company, when we begin talking about some of these
24 possible diagnostics, folks always come back and say, well,
25 you haven't identified a biomarker or you don't have any

1 activity. Where are you going to find a biomarker? So, I
2 think with vasculitis in particular, I would advise us to
3 be a little careful and perhaps refer to a diagnostic for
4 vascular injury with the hopes of finding a biomarker or
5 biomarkers.

6 The other thing that's problematic, I think, in
7 the area of vasculitis -- and you've touched on it as well
8 -- is that since there is not a biomarker or a diagnostic
9 for vasculitis in humans, most of us who study vasculitis-
10 inducing drugs cannot go so far as to do experiments in
11 humans where we can assess are the animal models a good
12 predictor of what's occurring in humans or vice versa.
13 There is an occurrence of vasculitis in humans that we
14 probably never would see in animals either.

15 So, I think one of the things this committee
16 could do is to maybe help bridge the gap of how do we get
17 from our knowledge preclinically of vasculitis-inducing
18 drugs, how do we do those exploratory kinds of activities
19 in humans, obviously without endangering humans. And I
20 think that's where we can have significant input into maybe
21 building those bridges or those collaborations.

22 DR. DOULL: But the methodology you're talking
23 about, a lot of that should be applicable clinically,
24 shouldn't it? The NMR, plasma, urinary things, proteomics
25 and so on?

1 DR. REYNOLDS: Yes. I would think of the
2 methods they referred to here or others, there's probably
3 not a method I've seen that isn't applicable in humans
4 under some circumstances.

5 DR. DOULL: Yes, Frank.

6 DR. SISTARE: There are definitely a lot of
7 issues to discuss here. I'm just wondering, with respect
8 to timing, do we want to take a short break now and come
9 back and discuss, or do we want to discuss for about a half
10 hour?

11 DR. DOULL: Okay, 10 minutes.

12 (Recess.)

13 DR. DOULL: I guess we're back on track. We're
14 now at the point to discuss the vascular injury.

15 Since the name is formally Vascular Injury, it
16 is no longer the Vasculitis Working Group. It is the
17 Vascular Injury Working Group. We need to have all our
18 records show that since we have made that change formally.

19 Okay, questions for Tom. Joy.

20 DR. CAVAGNARO: So, commenting again to Jack's
21 point, this is a huge and ambitious initiative and very
22 comprehensive, and if you do it by 2003, that will totally
23 amazing. But this is a real issue now. There are drugs in
24 development that are on clinical hold or various stages of
25 clinical partial hold or whatever. So, in efforts to move

1 forward in that regard, I'd be interested in some comments
2 on that.

3 The other point is the diagnosis now is based
4 much on histopathology data in animals, and whether or not
5 on your committee you have representation of veterinary
6 immunopathologists and human immunopathologists just
7 because I think there are some species differences in
8 animals that sometimes we call it vascular injury or
9 vasculitis. I don't know what we're calling it now. I
10 think that there are some differences, and to try to get a
11 handle on the significance of perhaps some species
12 differences.

13 So, I guess there were two questions. One,
14 what are we doing now for those products that we are
15 posting animals and seeing some findings and calling it
16 that? And then, two, making sure that we're understanding
17 potential species differences in how this syndrome is
18 presented.

19 DR. PAPOIAN: I could begin and then the other
20 panel members can take over.

21 As far as the current drugs go, until recently
22 findings of vasculitis in animals were considered to be
23 related to exaggerated pharmacologic activity. A new class
24 of drugs, the endothelial receptor antagonists, sort of
25 changed that in the sense that you can have vascular injury

1 in the absence of systemic hemodynamic alterations. This
2 has subsequently been shown. It was presented also last
3 week and was very interesting. It can occur either in the
4 absence of marked regional flow changes as well, which sort
5 of further shows the complexity and difficulties of using
6 any sort of analytical biomarker or any sort of test to be
7 able to monitor for such effects in humans. The idea was
8 that these sort of changes are unlikely to occur in humans
9 at therapeutic doses.

10 So, I don't know if that's the reason why other
11 divisions and other divisions throughout the center have
12 put drugs on hold for findings of vasculitis. I think they
13 were always doing that before, but previously if it could
14 be shown that these changes occurred with marked
15 hypotension and marked tachycardia, that these sort of
16 effects were unlikely to occur in humans and therefore
17 posed minimal risk. That's the current state of affairs
18 with drugs in the center for now.

19 I don't know if anybody has any comments to
20 that effect.

21 That's one of the things that holds up drugs
22 and why they are put on partial holds or in holds is that
23 people feel uncomfortable as far as how to be able to know,
24 to be able to monitor whether such effects are occurring in
25 humans or not, particularly when the drugs are not always

1 | cardiovascular drugs. They're not all vasoactive drugs.
2 | You can have other classes of drugs now that produce these
3 | lesions, and so it's not really clear what the mechanism
4 | is. The idea is they don't know whether these effects
5 | occur in humans or not.

6 | DR. SISTARE: You had asked about the working
7 | group makeup in terms of pathologists, and we do have a few
8 | on the committee. A number of industry representatives on
9 | the committee are bringing slides that their pathologists
10 | have diagnosed. David is on the committee and Fred Miller.
11 | They're clinicians clearly, but not human pathologists,
12 | clinical pathologists.

13 | Dr. Jun Zhang is actually trained. He's not
14 | formally on the committee but again, these people are sort
15 | of behind the scenes, but not formally on the committee.

16 | A couple other points.

17 | DR. PAPOIAN: Could I just make a quick point?
18 | Identifying lesions in humans is what currently does not
19 | exist. In other words, there are no lesions that have been
20 | ascribed in humans. So, it's not like one of those
21 | pressing issues that we have to have a clinical pathologist
22 | involved to be able to look at these sort of effects in
23 | humans and correlate whether these are the same things that
24 | occur in animals. I think maybe Dr. Essayan might be able
25 | to discuss as far as what drug-induced vasculitic lesions

1 occur in humans, but the mechanisms behind those are
2 obviously markedly different from what we see in animals.

3 DR. CAVAGNARO: I thought you said minoxidil
4 was.

5 DR. PAPOIAN: That's the drug where human
6 tissue was examined in people that were treated with
7 minoxidil for up to a year, and after they died, their
8 hearts were looked at to see if there was evidence of
9 vascular inflammation in the hearts. Even though there was
10 some vascular inflammation, some damage, it was thought to
11 be not related to drug. So, that's the only case where
12 human specimens have been looked at to correlate with
13 what's known to occur in animals.

14 Minoxidil is sort of a different story, because
15 the effects in animals occur -- it's a combination of
16 vascular inflammation, as well as myocardial necrosis. The
17 necrosis is thought to occur from the work overload from
18 the tachycardia that occurs as a result of the drop in
19 blood pressure. So, those sorts of effects are unlikely to
20 occur in humans. If that were to occur, they would be
21 given beta blockers, beta antagonists to prevent the
22 increases in heart rates. So, it's probably not
23 unreasonable to think that -- you know, it wasn't
24 surprising that lesions were not found, but it gave a
25 certain amount of reassurance that it's just not a toxic

1 effect, but it possibly could have been related to its
2 pharmacologic activity or the marked pharmacologic activity
3 that was seen in animals.

4 DR. CAVAGNARO: I guess I'm referring to some
5 of the cases where the preclinical data suggests some type
6 of a vasculitis-like syndrome, but it doesn't totally fit
7 to a human syndrome. So, then the question becomes, so do
8 you err on the conservative, which generally happens? You
9 err on the conservative I guess.

10 DR. ESSAYAN: Yes. I think to a large extent,
11 these are the issues that we're trying to deal with
12 prospectively, and it's difficult to comment on the
13 question that you're asking because that's the question
14 that we intend to ask through the research we're going to
15 do. We understand your cause for concern.

16 As far as a direct effect on the current
17 applications, I think we have to bear in mind where we are
18 with this committee. We've generated a series of short-
19 term goals where we're going to take the candidates that
20 we've already identified and try to set up collaborative
21 research efforts that would look into those. Our
22 probability of finding the magic marker or the magic
23 diagnostic from that group is relatively low, but these are
24 leads that we already have which we wish to pursue.

25 The emphasis of this group is really much more

1 on the long-term goals where we're going to embrace a more
2 far-reaching discovery mode using these different other
3 techniques to look for a pattern which may more
4 appropriately be called a diagnostic, and from that
5 pattern, either by NMR or proteomics/genomics type
6 technologies, potentially identify a specific biomarker
7 wherein we would be able to narrow down.

8 To what extent it's going to address mechanism
9 is unclear. The kinetics, also unclear. Its applicability
10 across the different types of injury that may be seen, also
11 unclear at this time. In a way, that's what makes this
12 particular committee exciting to me because we really don't
13 have a lot of answers and leads right now and the field is
14 very much open.

15 DR. SISTARE: It's tough to give one label. As
16 Tom pointed out, there's a lot of debate about what to call
17 this: vasculitis, vascular injury, vasculopathy. There
18 are sponsors who have drugs which cause an inflammation on
19 just the venous side. There are sponsors who have agents
20 which cause vasculitis on just the arterial side. There
21 are agents which kind of bridge the very small vessels, the
22 arterioles, the capillaries, the venules. There are agents
23 which cause vasculitis in just the mesenteric bed of the
24 rat. There are agents which cause vasculitis in the rat,
25 the dog, and the monkey. It's a huge spectrum.

1 And then there's IL-2 induced vascular leak
2 syndrome. Where does that fit? That's a sort of a
3 vascular injury. There's certainly an inflammatory
4 component, but there isn't blood coming out.

5 So, there's a very diverse spectrum of things
6 happening, and that does occur in the clinic, IL-2 induced
7 vascular leak syndrome. That does occur in the clinic.
8 So, there are a lot of questions here.

9 One of the first focal points is we see a
10 manifestation of this diverse class of injuries in
11 different species, different beds, and sponsors want to
12 develop this. It's otherwise a very good compound, no
13 other problems with it. This is the dose-limiting
14 toxicity. Well, if this dose is 100 times where they want
15 to go in the clinic, could it happen in the clinic? It's
16 still there in the back of your mind, but you're not so
17 concerned. But what if it's tenfold, what if it's
18 fivefold, what if it's fourfold, the blood levels that you
19 want to get to?

20 So, are we being too conservative in preventing
21 the introduction of compounds into the clinic, into
22 development that could be very beneficial on the one hand
23 because of this concern that we have no way of monitoring
24 for? Clearly if benefit outweighs risk and if you don't
25 know that there's a real risk, you make those kinds of

1 | decisions. Those kinds of difficult decisions are made by
2 | regulators and sponsors all the time.

3 | But what we need is we need something to shed
4 | some light on this very complex subject right now. We need
5 | to open up a new can of tools that we can use to measure
6 | something to tell us what's going on. Whether it's going
7 | to be mechanistic or whether it's going to be very
8 | proximate to the injury, both of those have value. Right
9 | now we just have nothing. So, we're not talking about an
10 | ideal biomarker. We're talking about something, some
11 | biomarker.

12 | So, the first data that I've seen, data that
13 | came out of our lab, data that came out of Boehringer's lab
14 | recently, agents were dosed and we found some inflammatory
15 | biomarkers. Now, some inflammatory biomarkers are good in
16 | some species, but the same ones are not good in other
17 | species. C-reactive protein, for example, is very good in
18 | humans and dogs, but it's not good in rats. Alpha-2
19 | macroglobulin is better in rats, but it's not good in
20 | humans. So, it's not a perfect biomarker, but at least
21 | it's something.

22 | Now, if you're going to use that drug to dose
23 | someone with an inflammatory disease, arthritis, it's not
24 | going to be the best biomarker because they're going to
25 | come up with high levels already. Or if they have some

1 | underlying viremia when they come into clinical trials,
2 | they catch a cold, you might see some inflammatory signals
3 | going on there. You don't know if it's drug-related or
4 | what. So, it's not the perfect biomarker, but it's a
5 | start.

6 | So, that's sort of the state of where we are
7 | with this. And what we're trying to do right now is keep
8 | the momentum going that's in the laboratories, as Tom
9 | pointed out, that there are laboratories that are doing
10 | things here. We're trying to keep our momentum going, but
11 | let's optimize what we do. Let's decide on one of the most
12 | important unanswered questions and which laboratories have
13 | technologies that they can tap into and the same samples
14 | generated from one study can be looked at in six different
15 | labs. If someone has the strength of flow cytometry to
16 | look at endothelial cell markers in the circulation, they
17 | can do that rather than five of the other labs trying to
18 | develop the methodology and get it in their lab. So, we're
19 | trying to optimize. So, that's one strategy, and that's an
20 | ongoing thing.

21 | But as Tom pointed out, the expert working
22 | group has a number of options we can consider that are
23 | going to take longer. Should we try to get NIH to get
24 | grants out there? Should we try to get ILSI involved?
25 | These are all questions that we have. How can we best

1 optimize this? Can we get other sponsors who are wrestling
2 with this issue to the table? Can we bring them to the
3 table as well in some sort of a collaborative mode without
4 ILSI involvement? Maybe that would be the quickest way to
5 do that. And how can we best do that? Set up a workshop,
6 for example. Publish in the Federal Register.

7 Because right now, I don't know. We have three
8 or four companies that are at the table with problems, but
9 I know there are other companies that are developing
10 compounds where they see this problem that are not at the
11 table. So, maybe we could somehow open it up and get them
12 involved in it. Again, if they're not willing to share
13 their compounds, maybe they can dose animals and then they
14 can share samples to other labs that can do specific
15 measurements.

16 Some people have monkey studies. We can't do
17 monkey studies. It would bust my budget to do one monkey.
18 But there are other companies that could do monkey studies.
19 Those are invaluable. The specimens you could generate
20 from that would be invaluable to test some of the
21 hypotheses.

22 DR. CAVAGNARO: Yes. I think a workshop is a
23 good idea actually.

24 DR. DOULL: History is on your side. I'm
25 thinking the problem you have really is sorting effects

1 | from toxicity. There are a lot of effects that we see in
2 | animals, for example, that are not predictive of toxicity
3 | either in animals or in humans. They are simply effects.
4 | But eventually, as one keeps massaging those effects, like
5 | P450, for example -- we knew about P450 years before we had
6 | any toxicity associated with P450. But eventually as we
7 | learn more and more about what those effects really mean
8 | and what they have to do with mechanism, somehow they get
9 | woven into the fabric of what really defines toxicity.

10 | And you're kind of that way with vascular
11 | injury. There are a lot of effects, and as you point out,
12 | they vary around species and they vary around agents and so
13 | on. But until all that comes together and you have a
14 | handle on it, I think it's hard for that to be particularly
15 | predictive.

16 | On the other hand, what else can you do? You
17 | have to start in that way, amass the information, and
18 | somehow try and make sense out of all that.

19 | DR. SISTARE: I'm not sure I'm interpreting
20 | what you're saying accurately. There's no one, I think,
21 | that would doubt that what we're seeing in these studies is
22 | toxicity. These are not effects. These are toxicities.
23 | We're seeing injury. We're seeing hemorrhage. We're
24 | seeing inflammation. So, there was no one who would doubt
25 | that this is toxicity.

1 When we measure changes in proteins in the
2 serum or when we measure changes in things in the urine,
3 those are effects. And you're right. To try to sort out
4 what are effects and what of those parameters that have
5 changed are toxicities, that's a real challenge. And when
6 we talk about a global approach that taps into genomics and
7 proteomics and metabonomics, those are very important
8 things that have to be sorted out.

9 In the working group, we have examples of
10 laboratories that have strain differences. So, you can
11 give the same dose and you can see pharmacology, but not
12 get vasculitis. Give the same dose to a different strain
13 of rat, get vasculitis. So, that's a nice tool to try to
14 sort that out.

15 Then there's also specificity questions, things
16 in similar classes that are not bad actors, these kinds of
17 things that we're using to sort out. And then there's
18 always dose ranges, those classical things.

19 You're right. It's going to take a lot of work
20 to get us to the point. I'm a little more optimistic that
21 we may have something prior to 2003 that won't be a
22 validated biomarker, i.e., along the lines of a troponin,
23 but it could probably be something that could be
24 incorporated in a developmental strategy that could be used
25 in the developmental strategy to get something from the

1 nonclinical/preclinical into phase I and to learn at that
2 point, to learn about the value of that biomarker, to
3 incorporate that into the clinical study. If you have
4 confidence, if the logic is there, you've done monkey
5 studies, you have dog studies, you've done rat studies,
6 everything fits into place, and now we'll say, okay,
7 measure this in your clinical trial. I think there's a
8 real learning opportunity, and it's something that won't
9 have like an ICCVAM blessing. You may not have a
10 diagnostic that's been approved by CDRH, but I think you
11 might have something that you can incorporate into a
12 clinical trial.

13 DR. DOULL: I think it will be a little slower
14 with proteomics and metabonomics than it will be for some
15 of the other things you're talking about.

16 Tom.

17 DR. PAPOIAN: Frank mentioned something that
18 was discussed with the working group about when would be an
19 appropriate time to monitor patients if an appropriate
20 biomarker or diagnostic was found to be predictive in
21 animals, and that would be to also minimize the background,
22 just not specific inflammation. And that would be possibly
23 with the phase I clinical trials as part of the normal
24 safety and tolerability studies where you can sort of
25 minimize background disease incidents. And these would be

1 healthy people free of disease, free of infections, and to
2 be able to see whether the drug would produce the same
3 changes that were found in animals, at least by the
4 biomarker status. So, as an initial screen to be able to
5 at least get into a clinic, they'd be able to find out at
6 least in healthy humans and find out whether the drug has
7 potential to produce the same sort of effects that were
8 found in animals.

9 DR. DOULL: It's cheaper to do it in rats than
10 in phase I.

11 Frank.

12 DR. SISTARE: I want to make one other point,
13 and I have to be really careful how I make this point. But
14 a paper came out recently in JAMA which talked about trying
15 to understand why certain people who were not otherwise at
16 risk for a myocardial infarction -- they didn't have high
17 lipids, these kinds of things -- yet had heart attacks, had
18 cardiovascular events. And they found that there was a
19 subset of patients that had elevated levels of
20 myeloperoxidase and IL-6, and these are markers associated
21 with inflammatory vessels. So, there's a logical link
22 there. So, the thinking of the article is that maybe
23 there's some inflammation that might be precipitating and
24 predisposing certain patients to cardiovascular risk, risk
25 of heart attack.

1 So, as we start and use animal models to
2 uncover and unravel what might be some good markers of
3 arterial inflammation, venous inflammation, vascular
4 injury, we may be able to ultimately work up a set of
5 endpoints that would be able to pick up patients or people
6 that might be very sensitive to these kinds of things and
7 ought to avoid certain things. We're focusing a lot on
8 genomics, SNP, these kinds of things to identify patients
9 that would be at risk, but I think as we develop the
10 biomarkers for looking at some of these insidious effects,
11 I think we're also going to be able to pick up responders
12 and nonresponders or cohorts of patients that might be very
13 sensitive to certain things and ultimately really improve
14 safety profiles of medications. There may be some people
15 that are very resistant to these things that can take a lot
16 and maybe open up markets.

17 So, these are things that we have to think
18 about I think in terms of expanding potential applications
19 of biomarkers and seeing where this thing leads. But I
20 think here and now the focus of this is we are in
21 situations where we have drugs in development and we don't
22 know how monitor, and we're being somewhat conservative
23 here. So, I think that has to be the focus. But there's
24 always potential leads.

25 DR. DOULL: Let me back up for a minute and go

1 back to what we talked about a little earlier and that's
2 ICCVAM. As I understand it, the whole focus of ICCVAM is
3 to find alternative testing, protocols, whatever that are
4 in fact predictive. One of the problems they have in
5 ICCVAM is what's the gold standard. If you develop a new
6 procedure, what are you really going to compare that
7 against? If we have a new test for cancer, for example,
8 you compare that against the NTP bioassay or whatever. And
9 how good are the gold standards in a sense?

10 It seems to me we're going to have this kind of
11 problem here also because Joy was asking what are you
12 really comparing the biomarkers or the effects you're
13 describing against in order to validate them, if I
14 understood. I guess what that says to me is that somehow
15 we need to be thinking about what ICCVAM is doing and
16 keeping track of how they're making progress in defining
17 gold standard biomarkers, if you will, or whatever they're
18 going to do that will help us.

19 That's always the response. When you talk to
20 those guys, you say, well, how does it compare with the NTP
21 bioassay, and everyone says, well, that's not so hot. The
22 rat doesn't predict for the mouse and neither predicts for
23 man. That's always a problem of what is the final really
24 test. Well, the final really test is does it predict the
25 right answer for man and do you have clinical data that, in

1 fact, validates the biomarkers somehow.

2 But ICCVAM must be dealing with these same
3 issues, I would think, Jim.

4 DR. MacGREGOR: The reason I mentioned ICCVAM
5 before -- well, let me just back I guess before ICCVAM.

6 I think when you come to the point where you
7 have a new biomarker and become convinced that it has
8 applications, then what you might recommend as a committee
9 or what the parent committee might recommend really depends
10 on the arena of applicability. So, if it's something
11 that's specific to drug development, obviously there could
12 be a recommendation to CDER for guidance. If it's
13 something that cross cuts FDA, there could be across FDA
14 FDA guidance. And then if it cross cuts other agencies,
15 then you need to start thinking about ICCVAM.

16 And then when you begin to think about ICCVAM
17 and biomarkers, I guess the way ICCVAM has operated in the
18 past in my mind has not really been focused on specific
19 biomarker application. It's more a whole new assay
20 approach. And the way they've gone about it has been
21 really a rather time consuming and slow process such that
22 over their history, they've really only addressed a very
23 few assay systems.

24 So, we in fact in the cardiotox group had some
25 discussion and invited Len Schechtman from ICCVAM in to

1 talk about ICCVAM and where it's going because it was felt
2 that it would be useful to have an organized multi-agency
3 group that could address biomarkers. But in my mind,
4 probably ICCVAM would have to change the way it goes about
5 its business a little bit in order to be able to do that in
6 an effective manner. That is, they might have to think
7 about establishing focused expert groups to just look at
8 the evidence on a particular biomarker where it might be
9 used, and they could do that perhaps in a fairly efficient
10 way, if they were to organize in that way, because they do
11 have the multi-agency structure. And the criteria are all
12 laid out, so all that background is done.

13 And I bring it up in part because our office is
14 heavily involved and because Len Schechtman, who is in our
15 office, is chairing the committee that is rewriting the
16 guidelines for how ICCVAM should be operating. So, I don't
17 know if the timing will come together or not, but if the
18 timing were to come together that this group could see a
19 way that ICCVAM could help develop broad recommendations
20 more efficiently, then some recommendations could even go
21 out in that regard.

22 But I wouldn't want to see this group get
23 diverted into that. It would only be if it made sense that
24 that would be the arena where it might go.

25 DR. SISTARE: My understanding of ICCVAM also

1 is that ICCVAM is an evaluation committee. All the work is
2 done. All the I's are dotted. All the T's are crossed.
3 All the data is there. It's submitted and it's either
4 blessed or it's not blessed.

5 So, what we're talking about here is we're
6 talking about developing the data. That's what's needed
7 here. Even with the troponin group, it's like where is the
8 data. At what point are we with the data? Is it at the
9 point where we're close to a final thing? And maybe if we
10 are, then we can go to ICCVAM with it as well in parallel.

11 But with this effort, we're talking about
12 calling the cavalry and saying we've got a problem. Who
13 can help us solve this? Who can help combat the enemy
14 here, and let's solve this problem. So, we're not ready to
15 talk about ICCVAM with vasculitis I don't think. We're not
16 close to it. Maybe at some point we will, but right now I
17 don't think we're there.

18 DR. DOULL: Yes. I'm not even sure we're close
19 with cardiotoxicity to talking to ICCVAM.

20 Well, ICCVAM has only approved one procedure,
21 haven't they, in all that effort they're doing?

22 DR. DEAN: There are actually three or four.

23 John, about ICCVAM and cardiotoxicity or the
24 troponins, if the test is a test that's been approved by
25 the FDA for clinical use, and you then apply it to the

1 animal, I'm not sure that would become part of the ICCVAM
2 process because ICCVAM is really, as Frank said, about
3 evaluating new test methods in animals to see if they're
4 applicable and have any predictive value and are they
5 reproducible, sensitive, et cetera.

6 The local lymph node assay was probably the
7 most classic example where you had conventional test
8 methodology in the guinea pig testing and now you had a
9 newer, more rapid test system in the mouse, and did they
10 give you equivalent data in terms of risk assessment or
11 hazard identification.

12 But if you take this area of vascular injury, I
13 mean, you're so far removed from anything you could
14 validate, that it probably doesn't fit.

15 But let's go back to your first point about
16 ILSI a minute. Both Ken and I are on this Emerging Issues
17 Committee, and in the conference call a month ago or less,
18 this was presented as a topic that people were very
19 enthusiastic about, at least on the committee, as something
20 that companies might be interested in helping with. And I
21 know in the January annual meeting, it will be proposed in
22 the Emerging Issues Committee as something for the
23 membership to see if they would be interested in
24 collaborating.

25 As you pointed out, I think ILSI is a nice

1 platform where you need to do work to get the industry and
2 academia and government people together to try to do work
3 and where you can put in sweat equity and the companies can
4 put in money, et cetera. So, ILSI could be a very
5 interesting platform for this kind of a fishing expedition.
6 Maybe fishing is not fair, but where you need some industry
7 people to do some work in some animals and share data.

8 DR. SISTARE: Yes. The issue came up at our
9 last expert working group meeting. Clearly the feeling was
10 that we have some momentum going now, we have some progress
11 going on. Let's build off of that, and maybe we can find
12 funding mechanisms with the academic representatives that
13 were there through individual partnerships with some of the
14 pharmaceutical companies. And they said, we see a very
15 focused question. You've got something you can do for us.
16 We'll find a way to make that happen. That was sort of the
17 dialogue. So, clearly that was said.

18 But then the issue came up -- because I believe
19 it was Bill who submitted the recommendation to ILSI, and
20 then Bill found out that, yes, this will be presented in
21 January. And there was some discussion about is that the
22 best thing or isn't that the best thing. I'm not exactly
23 sure how to say everything that was conveyed there, but
24 I'll try.

25 There is clear need to get very focused things

1 | done and try to do them as quickly and as expeditiously as
2 | possible. There was some concern that going through the
3 | ILSI -- I don't want to say bureaucracy, but the ILSI
4 | committee structures and everything and then formalizing
5 | the proposal and getting it all to big Pharma and then big
6 | Pharma coming back and saying yes or no, might take a lot
7 | of time. And it might dilute potentially some of the
8 | funding that could go into direct, focused efforts. Not to
9 | take away the real benefit that definitely come out of
10 | these ILSI efforts. They've had tremendous success, and I
11 | applaud all of that and I encourage that.

12 | So, I think it's something that could go on in
13 | parallel. We should probably proceed with that, but maybe
14 | something for the committee here to consider is what are
15 | the best mechanisms to make this effort succeed, to ensure
16 | success here.

17 | DR. DOULL: Jim?

18 | DR. MacGREGOR: Just maybe to reiterate the
19 | charges to the various groups, I think the charge to these
20 | two expert groups is very clear, and the charge is to,
21 | within the assigned area of damage, to identify what we
22 | need in terms of biomarkers, what we have, and if we're
23 | lacking information, to define what information we need and
24 | also to define for the parent committee mechanisms by which
25 | that information might be gained. So, I think it's really

1 a clear part of the charge to the expert groups that if you
2 find that a certain set of research is needed to get a key
3 bit of information, we'd like to see the expert groups come
4 back here with alternative ways of getting that done for
5 discussion and implementation.

6 The charge to the NCSS subcommittee is to serve
7 as a steering committee to any such projects that might
8 evolve, so that after the expert groups have really
9 identified what needs to be done and alternatives for how,
10 then it would, I think, be the charge of this subcommittee
11 to make some recommendations and to facilitate and serve as
12 a steering committee to the work to bring that information
13 back in in a form that then could become the basis of a
14 recommendation. And then recommendations would have to go
15 through a parent committee to FDA for implementation.
16 That's the way it should work.

17 DR. DOULL: Actually the Vascular Injury
18 Working Group has, in fact, done that. You are saying to
19 us you are envisioning some kind of a study for which you
20 would develop protocols and drugs and procedures and so on
21 that would provide you with some information about sorting
22 out biomarkers for vascular injury. And you talked in
23 there about ILSI and you talked about NPR, other sorts of
24 funding and so on. So, I guess in a sense we're at that
25 stage.

1 And the cardiotox. You have talked about some
2 activities that also would need funds.

3 So, I guess we're at a point where we need to
4 talk about how this subcommittee can help the working
5 groups take the next step, and the next step you're talking
6 about is really I think probably the budget. There are
7 some formalities about how you do things within the agency
8 and all, but budget is clearly an issue that we need to get
9 around to. I guess, Helen, I wonder is this the time to
10 move into that area because we're now talking about how
11 this committee is going to function to help the working
12 groups.

13 MS. WINKLE: I think Ken had a question first.
14 Didn't you have a question before we get into this topic?

15 DR. WALLACE: I was only going to make the
16 remark, as we were talking about formulating relationships
17 with ILSI, that the vasculitis has already ventured into --
18 I was just going to make the comment that the cardiac
19 injury group had also had the same discussions and is
20 considering those opportunities, whether we can set up a
21 synergistic relationship with ILSI and other organizations.
22 But we are really looking to the NCSS for guidance on how
23 to do that.

24 DR. DOULL: I might just mention that when we
25 were talking about looking at various biomarkers and

1 | looking at imaging and proteomics and all those things, we
2 | didn't go into the liver specifically, and one of the
3 | reasons was that ILSI already had a working group that was
4 | working on the liver and was developing all those topics.
5 | So, we thought that would be redundant. So, there is, in
6 | fact, in ILSI an established interest in that whole area of
7 | biomarkers, and they've talked about it at the meetings
8 | every now and then. So, clearly there's some history for
9 | ILSI there.

10 | Helen, why don't we go ahead and talk about --

11 | DR. MacGREGOR: Can I make one more comment
12 | about these funding mechanisms and organizations before we
13 | go into that?

14 | DR. DOULL: Sure.

15 | DR. MacGREGOR: We've had some other
16 | discussions also. I guess personally I would say I think
17 | we're very close, but I'm not sure absolutely ready to go
18 | out and try to bring in specific support because I think
19 | both groups are moving toward a set of recommendations for
20 | an approach, but I think in both cases there are not yet
21 | specific research proposals or even -- and I don't mean in
22 | the protocol sense, but I mean specifically what studies
23 | need to be done still remain to be defined.

24 | I guess there are a couple ways then you could
25 | go for resources and when. I guess my vision going into

1 | this was that the expert groups would identify very
2 | specific things that might be done and funding
3 | alternatives.

4 | As the discussions have gone on, I think a
5 | second line of thinking has now surfaced that maybe some of
6 | these organizations could be brought in and might be
7 | interested enough to put up money and help refine and
8 | define the questions. So, that's I guess something to
9 | think about.

10 | But the other thing I wanted to mention is
11 | we've had a lot of focus and talk about ILSI too, but I
12 | think FDA mechanisms are something that may also be
13 | available if things can be defined tightly enough. I am
14 | not sure if everyone on the subcommittee is aware, but the
15 | National Toxicology Program actually has a block of funding
16 | that's administered through the NCTR for the specific
17 | purpose of addressing major regulatory scientific needs of
18 | priority to the FDA. So, there's a mechanism there to
19 | bring science priorities that FDA considers its priority to
20 | NTP, which has got a funding block that's set up to conduct
21 | the work at NCTR. So, there's another mechanism to think
22 | about.

23 | Now, the way that system works, it would
24 | require I think a fairly specific plan because there's a
25 | priority committee that's set up for the utilization of

1 | those funds that essentially compares competing priorities
2 | and recommendations from the FDA centers and then decides
3 | what would make sense to fund. So, that's another thing to
4 | think about and talk about when we have a plan at that
5 | stage.

6 | DR. DOULL: I would make one point. One
7 | problem that we want to avoid is that we now have momentum
8 | in our working groups. They have had meetings. They have
9 | presented at the outside meetings and so on. Clearly that
10 | effort is recognized. It is moving forward, and we do not
11 | want this to bog down in the middle because of something
12 | that we have not considered, and funding certainly is one.

13 | One option would be to get all the funding from
14 | FDA, if that were possible. That would be one option.

15 | The thing that's wrong with that for me is that
16 | our charge says that our goal is to initiate joint efforts
17 | from industry, academia, and FDA. So, I think we need to
18 | think about joint efforts in terms of funding, joint
19 | efforts in terms of protocols, joint efforts in terms of
20 | what we do, and finally joint efforts in recommendations.
21 | And that means then that we would look around for money,
22 | not just from FDA.

23 | Helen.

24 | MS. WINKLE: I certainly agree with you, John.
25 | I think the emphasis has always been for collaboration to

1 have joint efforts in being able to get this research done.
2 You and I had a conversation during the break. I think one
3 of the things that we do need to take into consideration
4 that has always been an issue and a problem is that CDER
5 itself does not have the money to fund this research. So,
6 we have the laboratory support that we could do some of the
7 projects, but we definitely need to be thinking more
8 broadly in how we get these projects done. This was one of
9 the reasons for even setting up the committee, to be able
10 to do more collaboration, to get people involved in some of
11 these projects.

12 This brings me to the discussion we wanted to
13 have. I think last time that I met with the subcommittee,
14 we talked a little bit about moving this subcommittee under
15 the auspices of NCTR. And I wanted to talk a little bit
16 more about that. Jim is going to talk about it some.
17 Because I think it's important for you to know where we
18 are, and I think this is part of the budget issue as well.

19 I think it's very important to take into
20 consideration the fact that NCTR is budgeted to do
21 toxicological research and is very focused on this type of
22 research. As I said to John, the center is focused on
23 review. Obviously, in doing that review, there are
24 regulatory questions that come up that we need to be able
25 to answer, and we want to be able to do that through

1 research so that we have data to support our regulatory
2 decision making.

3 But let me go over again some of the issues
4 that I brought up last time as to why it would be
5 beneficial for this committee to be under the auspices of
6 NCTR, and then Jim can sort of catch you up with where we
7 are. I actually expected by this meeting that we would
8 have made some decisions, but we're still focused on coming
9 up with the appropriate way to handle this.

10 So, anyway, just to reiterate some of the
11 advantages of moving under NCTR. And one of the things
12 I've already mentioned, which is a real important
13 advantage, is the resources. The NCTR currently has the
14 resources to support the working groups, but also to
15 support the research under these programs and the projects.
16 I think what I've heard here today and I think what I've
17 heard in the past from this subcommittee is there are some
18 very significant projects that could be very beneficial in
19 moving head in the regulatory realm. And I think it's very
20 important that we make sure, as John said, we don't lose
21 the momentum. I think the expert groups have really moved
22 forward coming up with projects, and we want to be able to
23 support that. And I feel that NCTR, because of its focus
24 on toxicology, is in a better situation to do that than
25 CDER.

1 Also, I think, as we've already mentioned, the
2 ICCVAM process for the agency resides in NCTR, and if there
3 is some need for collaboration or some activities that
4 ICCVAM can help support in some of the projects we have, I
5 think that's important to be able to have that
6 collaboration.

7 I think also that the Science Advisory Board at
8 NCTR really has the scientific expertise to help support
9 these projects and help direct these projects. Although on
10 the Advisory Committee for Pharmaceutical Science, we
11 definitely have a toxicologist, John, that advisory
12 committee is not focused as much in toxicological problems
13 in general. Their focus is a little bit different, and I
14 think moving to NCTR would help benefit this group in being
15 better focused on those projects and issues and be able to
16 provide expertise and direction. They also have the
17 networking and more of the connections with the community
18 than obviously CDER is going to have or our advisory
19 committee.

20 Last of all, I think at least the last time I
21 talked to Dr. Casciano, there was a real desire to bring
22 this subcommittee together with NCTR, a science advisory
23 board, to better coordinate some of the science. I think
24 it's important, though, that CDER stay involved, and after
25 Jim sort of brings us up to date with where we are, I will

1 | talk a little bit more too about how I think CDER can keep
2 | that collaboration with this subcommittee, if it is, in
3 | fact, moved to NCTR, and how we can ensure that
4 | interactions are continued.

5 | So, I'm going to hand it over to Jim for a few
6 | minutes.

7 | DR. MacGREGOR: Well, thanks, Helen.

8 | I think Helen summarized very well kind of the
9 | FDA thinking, and we had quite a number of discussions
10 | within FDA about advantages and disadvantages of how we
11 | really might administer this group as it moves forward to
12 | really coming to the reality of developing collaborations
13 | and expanding and overseeing research projects and so on,
14 | which I think now is coming to fruition.

15 | So, the issues that Helen brought up actually
16 | have been brought to the NCTR Science Advisory Board for
17 | discussion. Basically their feeling, if I can summarize it
18 | -- and I'll say it's unfortunate that Ken Tindall couldn't
19 | be here because the plan today was to have Ken Tindall be
20 | here for this discussion to represent the NCTR Advisory
21 | Committee and to discuss the issues that they raised. So,
22 | he was scheduled to fly yesterday when the news was coming
23 | in and decided not to do that and volunteered to call in,
24 | but unfortunately, technically we were unable to hook him
25 | into the public record. So, therefore it wasn't possible

1 | to even bring him in by phone. So, I'll just have to try
2 | to summarize, as best I can, the input from that committee.

3 | So, their basic reaction was, yes, this makes a
4 | lot of sense. Scientifically this is where we are focused
5 | at NCTR. So, scientifically that makes a lot of sense.

6 | The major question that they had and the major
7 | concern about moving the committee between the advisory
8 | committees was they saw the importance of maintaining a
9 | connection with the important constituencies which are,
10 | namely, the pharmaceutical industry collaborators who
11 | historically have been tied closely to CDER and also CDER
12 | itself, which is a critical link.

13 | So, I think we have the situation that was
14 | plain to them that the regulatory science motivation kind
15 | of came out of the drug development arena, and then as we
16 | picked our focus areas and decided where we were going to
17 | go, those areas led us down a scientific path, namely
18 | biomarkers of safety, that happens to be a major scientific
19 | focus of the NCTR.

20 | So, I think the consensus is that NCTR has made
21 | the decision that it's focusing a major part of its
22 | resources in its research program in the biomarkers area
23 | and that it does have a science board that has in-depth
24 | scientific knowledge of the toxicology issues, which would
25 | make a good sounding board body for the recommendations