

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

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ADVISORY COMMITTEE FOR PHARMACEUTICAL SCIENCE

NONCLINICAL STUDIES SUBCOMMITTEE

+ + + + +

MEETING

+ + + + +

THURSDAY

MAY 3, 2001

+ + + + +

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ORIGINAL

The meeting came to order at 8:00 a.m. in the CDER Advisory Committee Conference Room, 5630 Fishers Lane, Rockville, Md., John Doull, M.D., Ph.D., Chair, Presiding.

Present:

- John Doull, M.D., Ph.D., Chair
- Gloria Anderson, Ph.D., Member
- Jay Goodman, Ph.D., Member
- Joy Cavagnaro, Ph.D., Member

Government Participants:

- Nancy Chamberlin, Pharm.D., Executive Secretary
- Daniel A. Casciano, Ph.D., Center Director, NCTR
- David Essayan, M.D., FDA
- James T. MacGregor, Ph.D., Deputy Director for Washington, NCTR
- Frank D. Sistare, Ph.D., Director Scientist, FDA
- Helen N. Winkle, Acting Director, OPS

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C-O-N-T-E-N-T-S

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Dr. John Doull (Chair)	
Conflict of Interest	3
Nancy Chamberlin, Executive Secretary	
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P-R-O-C-E-E-D-I-N-G-S

(8:34 a.m.)

1
2
3 CHAIRPERSON DOULL: Good morning. Let me
4 welcome you to this meeting of the nonclinical
5 subcommittee. This is kind of a red letter day for
6 us, we have been engaged in undertaking this project
7 for almost a year now, I guess, and it is now off and
8 running and we are here to celebrate that event and to
9 facilitate the formation of these two new working
10 groups.

11 We need to start out by doing the conflict
12 of interest activity and Nancy Chamberlin, you'll do
13 that.

14 DR. CHAMBERLIN: The following
15 announcement addresses the issue of conflict of
16 interest with regard to this meeting, and is made part
17 of the record to preclude even the appearance of such
18 at this meeting.

19 Since the issues to be discussed by the
20 subcommittee at this meeting will not have a unique
21 impact on any particular firm or product, but rather
22 may have widespread implications with respect to an
23 entire class of products in accordance with 18USC
24 Section 208(b), waivers have been granted to John
25 Doull, M.D., Gloria Anderson, Ph.D., Jay Goodman, Ph.D

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1 and Joy Cavagnaro, Ph.D. A copy of these waiver
2 statements may be attained by submitting a written
3 request to the FDA's Freedom of Information Office,
4 Room 12A-30 of the Parkland Building.

5 With respect to the FDA's invited guests,
6 there are reported affiliations which we believe
7 should be made public to allow their participants to
8 objectively evaluate their comments. Paul Snyder,
9 DMV, Ph.D would like to disclose that he owns stock in
10 Pfizer. He also is the principal investigator on a
11 proposal to study vasculitis in beagle dogs and has
12 received a privately funded grant to study vasculitis
13 in beagles.

14 Scott Burchiel, Ph.D is a part time
15 consultant to Boehringer-Ingelheim and a principal
16 investigator on a Boehringer-Ingelheim funded study of
17 flow cytometry, detection of vasculitis biomarkers in
18 dogs. Dr. Burchiel is also working on a project
19 involving vasculitis biomarkers in rats. Boehringer-
20 Ingelheim is funding the study through CRADA.

21 Lastly, William Kerns, DVM would like to
22 disclose that he has interests in SA Pharmaceuticals
23 and OmniViral Therapeutics and Camvite
24 Biopharmaceuticals.

25 In the event that the discussions involved

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1 any other products or firms not already on the agenda
2 for which any FDA participant has a financial
3 interest, the participants are aware of the need to
4 exclude themselves from such involvement and their
5 inclusion will be noted for the record.

6 With respect to all participants we ask,
7 in the interest of fairness, that they address any
8 current or previous involvement with any firm whose
9 products they may wish to comment upon.

10 CHAIRPERSON DOULL: Does the committee
11 have any comments, questions, about conflict of
12 interest?

13 Well, before we hear from our
14 distinguished guests, I think it probably would be
15 worthwhile to go around the room so that everyone
16 knows everyone, so let's do that. Let's start up
17 here. Nancy?

18 DR. CHAMBERLIN: Okay. We have new mikes
19 and for them to work you press the talk and the red
20 light comes on for these. And for these for when our
21 guests speak over here they're supposed to turn the
22 two buttons on the microphones is all I'm going to
23 say. Okay.

24 I'm Nancy Chamberlin, I'm Executive
25 Secretary.

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1 CHAIRPERSON DOULL: I'm John Doull. I
2 chair this committee. I'm from KU Med. Gloria, do you
3 have a mike?

4 MEMBER ANDERSON: Gloria Anderson,
5 Callaway Professor of Chemistry at Morris Brown
6 College in Atlanta, Georgia.

7 MEMBER GOODMAN: Jay Goodman, Department
8 of Pharmacology and Toxicology, Michigan State
9 University.

10 MEMBER CAVAGNARO: Joy Cavagnaro, Access
11 Bio.

12 DR. ESSAYAN: David Essayan, Center for
13 Biologics Evaluation and Research, Food and Drug
14 Administration.

15 DR. MACGREGOR: Jim MacGregor from the FDA
16 National Center for Toxicological Research and I'm the
17 FDA coordinator for the subcommittee.

18 DR. SISTARE: I'm Frank Sistare from the
19 Center for Drug Evaluation and Research in FDA.

20 DR. CASCIANO: Dan Casciano from the
21 National Center for Toxicological Research FDA.

22 CHAIRPERSON DOULL: Why don't we then
23 start back over here.

24 DR. ESSAYAN: For people on the expert
25 groups it would be useful if you identify which of the

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1 groups you're on.

2 DR. BURCHIEL: I'm Scott Burchiel from the
3 University of New Mexico and I'm on the vasculitis
4 working group.

5 DR. HERMAN: Gene Herman from the FDA's
6 Center for Drug Evaluation and Research, I'm on the
7 cardiovascular toxicity group.

8 DR. HOLT: I'm Gordon Holt from Oxford
9 GlycoSciences and I'm on the cardio tox group.

10 DR. BLANCHARD: Kerry Blanchard from
11 Boehringer Ingelheim and I'm on the vasculitis working
12 group.

13 DR. ROSENBLUM: Irwin Rosenblum, Schering-
14 Plough and I'm on the cardiovascular.

15 DR. SCHWARTZ: I'm Les Schwartz from Glaxo
16 SmithKline on the vasculitis group.

17 DR. METZ: I'm Al Metz from Pfizer and I'm
18 on the cardiotoxicity working group.

19 DR. MURPHY: I'm Elizabeth Murphy from
20 NIEHS in North Carolina and I'm on the cardiotoxicity
21 working group.

22 DR. MILLER: Fred Miller, Environmental
23 Autoimmunity Group, NIEHS, vasculitis working group.

24 DR. SNYDER: I'm Paul Snyder from Purdue
25 University on the vasculitis working group.

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1 DR. ROBERTSON: Don Robertson from Pfizer,
2 I'm on the vasculitis working group.

3 DR. YORK: Malcolm York from Glaxo
4 SmithKline, I'm on the cardiotoxicity working group.

5 DR. WALLACE: Ken Wallace, University of
6 Minnesota, I'm on the cardiotoxicity working group.

7 DR. KERNS: Good morning. Bill Kerns,
8 Pharma Consulting on the vasculitis group.

9 DR. NAGARKATTI: I'm Prakash Nagarkatti
10 from the Medical College of Virginia, I'm studying on
11 the vasculitis group.

12 CHAIRPERSON DOULL: One of the committee
13 members, Ray Tennant, is not here. He's from NIEHS.
14 I think that's all our members.

15 Well, it's a pleasure then for me to
16 introduce Helen Winkle. She is the acting director of
17 the Office of Pharmaceutical Sciences. Dr. Winkle.

18 DR. WINKLE: It certainly is my pleasure
19 to welcome the subcommittee. As Dr. Doull said, we've
20 been trying to get this committee up and running for
21 at least a year and probably even more years than that
22 at FDA. It goes back several years. And so it really
23 is an exciting day to start moving forward with the
24 expert working group. I really see that this is a
25 significant group. There's a lot that they can offer

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1 to the Center for Drug Evaluation and Research and I'm
2 really excited about the potential here.

3 This morning I just want to talk quickly
4 about NCSS and where it has been, where it is now and
5 where it is going next. But, first, let me take a
6 minute and just go back to the Advisory Committee for
7 Pharmaceutical Science and I'm doing this because I
8 want to put the subcommittee in sort of perspective as
9 to how it functions within the scope of the center.

10 The ACPS, or the Advisory Committee for
11 Pharmaceutical Science, serves the role of scientific
12 advisers to the Office of Pharmaceutical Science on
13 various complex scientific issues which affect how we
14 make our regulatory decisions. And the members of
15 these committees, Dr. Doull and Dr. Anderson are both
16 on this committee, serve a variety of different
17 scientific disciplines and they help with these
18 recommendations.

19 The various areas that the disciplines
20 include are for biopharmaceutists, for chemists, for
21 clinical pharmacologists, for toxicologists, there are
22 also microbiologists on this committee, and we look at
23 a variety of issues in these scientific areas.

24 We have over the years looked at a variety
25 of issues that have been brought before the committee.

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1 These issues include things like individual
2 bioequivalents for pharmaceutical products and
3 determining biopharmaceutics.

4 We've looked at dermatopharmacokinetics,
5 we've looked at biopharmaceutics classification system
6 which in the last year was just published in a guide,
7 and we've also looked at the reduction of CMC review
8 requirements. So we've brought a lot of issues before
9 this committee and what we're hoping to be able to do
10 was what the expert working groups do through the
11 subcommittee is bring these issues, or the issues you
12 identify and the research issues you identify, we hope
13 to bring those into the advisory committee and make
14 some decisions along the regulatory lines.

15 Next slide. Let me just go quickly now on
16 the NCSS and where we've been. Basically, and I think
17 many of you here know this, NCSS was actually an
18 offshoot of the CDDI and CDDI was a collaboration on
19 drug development improvement. It was a collaboration
20 that was started several years ago to bring academia,
21 industry, and the government together to make
22 decisions on the development of pharmaceuticals, and
23 its goals were basically to study and advance current
24 and new approaches to substantially improve the
25 efficiency of drug development and the review

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1 processes.

2 And one of the original committees of CDDI
3 was the nonclinical studies technical committee. And,
4 basically, CDDI didn't make it. It was one of those
5 areas where we had a real difficult time moving
6 forward with the different things that we wanted to do
7 in CDDI, but the NCSS did survive. I mean we all
8 agreed that this was a very important thing and
9 through the perseverance of Dr. MacGregor the
10 committee survived. We brought the goals of that
11 committee into the subcommittee and what you see now
12 is an offshoot of that.

13 I wanted to show you just quickly the drug
14 development process so you would understand where this
15 committee sort of fits in the overall picture. And
16 I thought this was an excellent slide because it shows
17 the various phases of drug development. It show the
18 preclinical research, the clinical studies, and
19 finally the NDA review and you can see from this that
20 basically we're talking about the preclinical research
21 here, and this is the significant foundation for them
22 bringing a product through the clinical studies and
23 the NDA review.

24 So what we're doing here in this
25 subcommittee and subsequently within the working

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1 groups, is extremely important as we move forward in
2 making our regulatory decisions. Next slide.

3 Basically, and I've already said this, the
4 purpose of NCSS is to serve to develop recommendations
5 on drug development approaches in the nonclinical
6 area. Next.

7 And the objectives are to provide advice
8 on improved scientific approaches to nonclinical drugs
9 development to the advisory committee, and to help
10 foster the scientific collaboration among FDA,
11 industry, academia and the public. And, again, this
12 is what the original intention of CDDI is that
13 intention continues to be fostered here within the
14 subcommittee and the working groups.

15 Just quickly where the focus of the
16 working groups and that's already been made clear as
17 we went through to see which working group everyone
18 was one, is for biomarkers for cardiac toxicity and
19 biomarkers for vasculitis. We see these as only the
20 first of the working groups, I'm sure there are other
21 issues that are going to come along over the years and
22 will include working groups for those issues as well.
23 Next.

24 I wanted to go through the next steps real
25 quickly just to show you where we are going. I think

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1 the important thing here today, and tomorrow, is for
2 the working groups' agenda to be finalized, for our
3 direction to be set with the working groups.

4 Then in July we will have an ACPS meeting
5 and the subcommittee will report back to the ACPS on
6 where we're going and the progress of the working
7 groups.

8 But, at the same time, we're looking at,
9 and this is an internal discussion that we're having,
10 is to closing out the subcommittee as part of the ACPS
11 and actually moving it into NCTR. We feel that the
12 emphasis of what we're doing here in the working
13 groups, although they affect the drug areas, also go
14 hand in hand with what is happening in the National
15 Center for Toxicological Research and, of course, that
16 has been facilitated by Jim moving to that center. So
17 we're in the process of making some decisions on how
18 we want to handle that, so we're looking at probably
19 in the fall, NCTR taking over the administration of
20 the subcommittee but, again, those issues are still up
21 in the air.

22 But, regardless of where the subcommittee
23 is in the future, it's very important that NCTR and
24 NCSS work closely with CDER to determine the issues
25 which are most important as we move forward.

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1 So that's basically, I just wanted to give
2 you a real quick overview of yesterday, today and
3 tomorrow and I want to wish all of you the best of
4 luck. I really look forward to hearing where you're
5 going with your working groups and I appreciate all of
6 your commitment to this group. Thanks very much.

7 CHAIRPERSON DOULL: Thank you. You heard
8 that clear message of support from the Agency for what
9 has happened and what's going to happen with these
10 working groups.

11 Let's move then to discussion of the FDA
12 objectives and role in what it is we're doing, and Dr.
13 MacGregor is going to give that.

14 DR. MACGREGOR: Well thanks, John. As
15 John and Helen have both said, I think this is a
16 landmark meeting of the subcommittee because there's
17 a lot of history that Helen went over briefly, and in
18 a moment I'll go back over some of that history and
19 kind of try to give you a little bit more
20 comprehensive feel about the discussions we've had and
21 the objectives and where we think we're going as a
22 subcommittee.

23 So, as I've said, the primary focus of
24 this meeting is to really now establish functional
25 working groups that really come to grips with the

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1 practicalities of the scientific issues that we'd like
2 to address and make progress in. And so we're going
3 to spend, we have two days scheduled for the expert
4 working groups, or a little more than a day and a half
5 actually, we're going to spend this first morning with
6 the subcommittee, delineating a little bit of history,
7 laying out the expectations of the subcommittee and
8 providing then an opportunity for both public comment
9 and questions and discussion between the expert group
10 members and the subcommittee and the public, and
11 anyone else that would like to comment, to be sure
12 that we all have a common understanding of our goals
13 and what we're trying to do.

14 And then when we finish with that, the
15 expert groups actually will go to work and they'll
16 work individually as the two expert groups, meeting
17 separately through lunch time tomorrow, and then after
18 lunch they will come back together in a plenary group
19 to report back to a joint meeting of the two expert
20 groups together what they've accomplished, where they
21 think they're going and what the next step should be.

22 So I'll go through those things in a
23 little bit of detail. And then I'm going to call on
24 Frank Sistare to give a little bit of the scientific
25 background and rationale that brought us to these two

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1 particular expert groups as the first groups that we
2 put together to move toward our goals.

3 I'd also though before I get into that,
4 like to just spend a couple of minutes on logistics,
5 just to lay out the plan for the day so everybody
6 knows what they're doing and where they're going and
7 how to get food when the appropriate time arises.

8 I think everybody on at least the
9 subcommittee and the expert groups has received a copy
10 of this map of the local area. If anyone has not,
11 either Nancy or Brenda Gomez, ah okay, over here, can
12 provide you with copies of this. If you have that, if
13 you want to pull that out right now I'll tell you some
14 things about the logistics of where we're going to go
15 and meet during the day.

16 So you've all managed to find the advisers
17 and consultants meeting room which is here, that is on
18 your map, and if you'll find that our plan is we're
19 scheduled to run through noon today, although I
20 suspect that we may finish up a little bit earlier
21 than noon.

22 And then we're scheduled to begin working
23 group meetings at one o'clock, so our plan is to
24 simply walk to the Parklawn cafeteria for an informal
25 lunch after we finish, whenever that might be. This

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1 is on your map and the way you get it is you go out
2 this door right here to the parking lot, turn left and
3 you'll be facing an obvious entrance to the Parklawn
4 Building on your left across the parking lot. If you
5 go through the security at that entrance, you'll be
6 standing right in front of the cafeteria and there are
7 a lot of large group tables there and we can just all
8 get our lunch and we can commandeer a few tables and
9 be able to meet and talk among each other.

10 Then at one o'clock, if you ask either one
11 of us from FDA or the security people outside the
12 cafeteria to direct you to the main lobby of the
13 Parklawn Building, directly across the street from the
14 main lobby, across Fisher's Lane, we'll have some cars
15 available for those of you that are on the vasculitis
16 group to bring you to your meeting room. The
17 vasculitis group will meet at the Ramada Inn, the
18 cardiotoxicity group will meet back here in this very
19 same room that we're in.

20 So if you're on the vasculitis group, or
21 if you're not on the vasculitis group and you'd like
22 to attend and listen to the proceedings of that group,
23 everyone is welcome to do that and I'll talk a bit
24 about the logistics of how the meetings will be run in
25 a moment.

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1 If you go out there at one o'clock we'll
2 have some transportation available to bring you over
3 there.

4 Then for dinner tonight we have an
5 informal dinner planned at the restaurant called
6 That's Amore, which is directly across Rockville Pike
7 from the Doubletree Hotel. I think most people are
8 staying at either the Doubletree or the Ramada and
9 this restaurant is just a few steps from either hotel.
10 So we'll convene there for a seven o'clock dinner and
11 we'll need to get a count, and maybe we can do that
12 right now, of the approximate number of people that
13 would be joining us for that dinner.

14 We have space available and maybe we could
15 just have a show of hands right now for people that
16 would plan to attend that dinner tonight at seven.
17 Okay, got it.

18 Okay. Now tomorrow we will continue with
19 working group meetings and, again, they'll be meeting
20 in the same places so those of you can easily walk
21 over to the Ramada, and if you like a brisk walk over
22 here in the morning you could do that or we can
23 discuss at evening if people would like to ride over,
24 we probably can find a couple of people to drive
25 people over in the morning from the Doubletree.

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1 DR. CHAMBERLIN: If there's a few people
2 that need to switch hotels because we book them at two
3 different hotels, I can help you transport your
4 luggage prior to lunch time.

5 DR. MACGREGOR: Okay, so if you need to do
6 that catch Nancy this morning and let her know.

7 Now everyone should have picked up outside
8 the two agenda, there are actually two separate
9 agendas, one for this meeting and one for the expert
10 group meeting so if you didn't get those two, they
11 look like this. Make sure you get one at the break.

12 Okay, any questions or comments about
13 logistics?

14 Okay. So what I'd like to do now is I'd
15 like to just provide a little bit more background on
16 this subcommittee and the objectives of the
17 subcommittee and these two new expert groups that have
18 just been formed. Next slide.

19 I think the general concept of this
20 committee is really that that's illustrated in this
21 slide, and that's to address the question of really
22 how should FDA be focusing its resources and
23 partnering in a way that leverages the resources that
24 are available in order to capitalize on new scientific
25 opportunities and bring those opportunities to a

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1 practical application in the regulatory process.

2 And so to that end, we've created this
3 subcommittee and the general concept here, I think, is
4 one that if successful could be expanded well beyond
5 this particular advisory committee. And the general
6 concept that is perhaps all of the focus the advisory
7 committees could assign a subcommittee of people to
8 address these general questions of what might be
9 improved scientific approaches, in this case to
10 nonclinical drug development and in the case of other
11 advisory committees to their particular functions.

12 And then to go a step beyond just
13 providing that advice and actually to play a role in
14 helping to foster and facilitate scientific
15 collaborations among FDA, industry, academia and the
16 public, to bring these ideas and approaches to
17 fruition. So that's the basic idea and the basic
18 thing that we're trying to achieve.

19 Now, as Helen has already gone over, the
20 specific objectives of this committee, the nonclinical
21 study committee, is to recommend approaches and
22 mechanisms to improve nonclinical information for
23 effective drug development that could improve the
24 predictivity of nonclinical tests for human outcomes,
25 and that could provide a linkage between nonclinical

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1 and clinical studies.

2 And then, importantly, in addition to
3 making these recommendations and providing advice, to
4 actually play a role in facilitating collaborative
5 approaches to advancing the scientific basis of drug
6 development and regulation.

7 Now Helen's already gone over some of the
8 early history and, as she said, it began with the
9 concept of the collaboration for drug development
10 improvement and eventually came to fruition with the
11 formation of this nonclinical study subcommittee as
12 part of the advisory committee for pharmaceutical
13 science.

14 This is a history of the subcommittee, the
15 subcommittee actually first met informally in August
16 of 1999 to develop the concept, discuss the rationale
17 and advisability of forming such a subcommittee. The
18 group that met, as Helen said, was really a spin-off
19 from the CDDI and included all the people that had
20 been involved in the CDDI nonclinical study
21 subcommittee.

22 People universally though it was a good
23 idea and so in September of 1999, the concept was
24 presented through the advisory committee for
25 pharmaceutical science, which endorsed the concept.

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1 Then in December of 2000, the subcommittee met and at
2 that meeting selected two general areas of focus that
3 it felt would be fruitful to pursue, and that was the
4 area of accessible biomarkers of toxicity and non-
5 invasive imaging approaches. And the reason the non-
6 invasive imaging came in was that it was felt that as
7 biomarkers were identified and developed that
8 eventually in order to be able to conduct the human
9 studies that would be necessary to link the
10 nonclinical together with the clinical, that
11 eventually imaging technology might be brought into
12 play in combination with molecular biomarkers to be
13 able to make analogous studies in the human to link
14 the nonclinical information.

15 Then in March the committee met again and
16 discussed how it might proceed more specifically
17 within these two general areas. And, at that time, it
18 was decided that we should focus in two very specific
19 areas, bring together experts in those areas, and then
20 try to formulate a specific plan with those areas to
21 see how the whole process worked. And the two focus
22 areas that were selected then at that meeting were
23 cardiotoxicity and vasculitis, that led to the
24 solicitation for nomination for these two expert
25 groups and then the selection process which I'll talk

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1 about in a little more detail.

2 Now, just back to the general picture, the
3 current groups that are actively participating in the
4 subcommittee and that have representatives sitting on
5 the subcommittee are listed on this slide. The
6 initial concept began with two of the FDA centers,
7 CDER and CBER, the initial CDDI steering committee was
8 composed of the two center directors from CDER and
9 CBER, as well as representatives from PhRMA, from BIO
10 and from academic institutions.

11 As we began to talk about FDA's role and
12 the impact of the activities of this committee on FDA,
13 it became apparent that we were moving toward
14 nonclinical toxicology studies and that NCTR should be
15 included, and they were added. It became clear that
16 NIH had many activities in the area of molecular
17 biomarkers and that they should be included, and Ray
18 Tennant was added during the past year to the
19 committee as the NIH representative and Ray is also
20 the chair of the new national toxicogenomics program
21 that's part of NIEHS and NTP.

22 So, hopefully, we've established a good
23 linkage there between the activities of this committee
24 and the national toxicogenomics program.

25 Now, these are the two meetings that I've

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1 already mentioned. Actually, I guess I've already
2 gone over this. I think we can skip this, I think
3 I've already gone over that one.

4 Now, the next two slides I think are
5 really key slides. These are the things we need to
6 focus on today and be sure that we all really have a
7 clear and common understanding. And this is, what's
8 the role of the subcommittee, what's the role of the
9 expert groups, and what does each expect the other to
10 be achieving?

11 So this slide deals with how we envision
12 the role of the subcommittee. And we see the role of
13 the subcommittee as being comprised of people from the
14 various stakeholder groups involved in initially
15 pharmaceuticals, although as Helen said, we're now
16 beginning to think about possibly even expanding
17 beyond that area in the near future. But within those
18 areas people that would be involved in the process,
19 knowledgeable about the science and the area and able
20 to identify and recommend those key focus areas where
21 activity should be focused.

22 In terms of mechanism, it's recognized by
23 the subcommittee that the subcommittee itself does not
24 contain all the technical expertise necessary to
25 really identify all the specific opportunities and

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1 formulate specific plans and approaches, and so the
2 subcommittee recognized that it would need to form
3 expert working groups to develop specific options.

4 And the process for that is something we
5 just have gone through with these two committees, was
6 to announce as widely as we could the opportunity to
7 serve on these groups, and to that end there were
8 announcements in the Federal Register. We approached
9 people on the subcommittee and the groups that are
10 involved in the activities and asked them to nominate
11 individuals, and we specifically wrote to and
12 solicited nominations from a number of professional
13 societies.

14 So with that process and with the expert
15 groups in place, the subcommittee would then serve as
16 the steering committee to oversee the expert groups,
17 the expert groups will be reporting back to the
18 subcommittee, and that should this whole process lead
19 to collaborative processes, then the subcommittee is
20 envisioned as the steering committee that would
21 oversee these collaborative projects, and the body
22 that would support workshops, reports, output from the
23 various activities.

24 Now the expert groups, as I've already
25 said, are experts within the areas specifically

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1 identified by the subcommittee, and the role of the
2 expert groups is to identify specific scientific
3 opportunities that could improve our regulatory
4 methods and regulatory approaches. To decide, within
5 those opportunity areas, what information is really
6 needed to translate the opportunity into regulatory
7 practice, to lay out some specific plans about how
8 that could be achieved, to think about resources and
9 expertise that would be needed to implement the plans
10 and identify those to the subcommittee. And, again,
11 to think specifically in terms of appropriate
12 collaborators, individuals, resources that could
13 actually bring things to fruition.

14 So the whole focus here is to try to be
15 practical and proactive and to think beyond just
16 advice. We don't want to just hear wouldn't it be
17 nice if we could measure all the relevant biomarkers
18 in both animals and human and that would be great.
19 What we really want from the expert groups are
20 specific opportunities and specific identification of
21 specific ways in which those opportunities could in
22 fact be brought to fruition.

23 This is just an expansion, really for the
24 record, of how we went about the identification and
25 recruitment of these groups. Following the meetings

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1 that I indicated in July of this year, the Federal
2 Register Notice published and essentially
3 simultaneously letters went out to scientific
4 societies, announcements were made within FDA,
5 subcommittee members made contacts and announcements
6 were made at public meetings to recruit nominations.

7 And then an FDA committee was formed with
8 representation from CDER and CBER and NCTR and
9 appropriate individuals within those groups involved
10 in the areas of the expert groups, that then reviewed
11 the applications and selected the membership, with
12 attention to achieving a balance among the various
13 constituency groups to be sure that we had
14 representation from all the areas.

15 Now, in terms of process and this is what
16 we're going to implement beginning this afternoon, as
17 I've already said, the expert group will be reporting
18 to the nonclinical study subcommittee, hopefully we've
19 provided guidance to you on what we'd like to have
20 from you. If that's not clear, that's what this
21 morning is for. Ask questions and be sure we go out
22 of this meeting with a common understanding of what we
23 want to achieve.

24 Then you, as working groups, need to
25 define your own milestones, when you're going to

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1 produce your report and so on. The expert groups may
2 meet independently of the subcommittee and the full
3 advisory committee, you're a working group, you
4 identify facts for the subcommittee and the full
5 advisory committee, those are the groups that actually
6 make recommendations to FDA.

7 We encourage you to solicit external
8 input. As I've already said, I hope we can keep the
9 expert group meetings open to interested parties as
10 much as we can, so that people can come. I think it
11 will be up to the chairs of the expert groups to be
12 efficient and to decide if it may be necessary to
13 limit discussion just to the working group in order to
14 move along, and that I think can be done on a
15 judgmental basis by the chair. And I think leaving it
16 up to the working group to form its own working
17 process and milestones and select its own chair, who
18 would then be responsible for providing summary
19 minutes of all meetings to the subcommittee.

20 Okay. So that's essentially the
21 background on the history, what we're trying to
22 achieve and so on, and now I'm going to go to Frank
23 Sistare and ask him to provide some scientific
24 background on what led us specifically to these two
25 groups.

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1 Are there any -- should I take any
2 specific questions at this point, or should I, does
3 anybody have any question or comment?

4 DR. SISTARE: It just might be helpful to
5 know can the expert working groups meet without
6 advertisement in the Federal Register ahead of time?

7 DR. MACGREGOR: Yes. I thought I had said
8 that but I'll repeat that. Part of our process here,
9 you know, I mean we spend a lot of time thinking
10 within FDA how we can meet all the requirements for
11 public availability of information, input from all
12 stakeholders, and still be able to get something done
13 in a timely fashion because, as those of you that have
14 been involved with advisory committees know, there are
15 many requirements. Everything has to be public,
16 advisory committees cannot even meet unless everything
17 is previously announced in the Federal Register and so
18 on and that takes a lot of time.

19 So we've looked a lot into these operating
20 processes. The expert groups may meet on their own,
21 without public announcement, although we do encourage
22 and hope that to the extent possible, the meetings
23 will be announced and that interested parties will be
24 able to attend and hear what's going on.

25 Then the expert groups will report back

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1 their proceedings to this subcommittee, and that all
2 must be part of the public process. So everything
3 they do will immediately get reported back to the
4 subcommittee and that will all be part of the public
5 process announcement in the Federal Register and so
6 on. And there'll be full minutes of those meetings,
7 whereas the expert groups may meet and just provide
8 summaries of their conclusions and proceedings.

9 Now, if I've misstated, and I see Nancy
10 leaning at her microphone and I've probably misstated
11 something.

12 DR. CHAMBERLIN: We will advertise expert
13 working groups, like we did this one, in the FDA
14 calendar events, not in the Federal Register.

15 DR. SISTARE: As Jim pointed out, he asked
16 me to give just like a ten minute overview of some of
17 the scientific issues, how we got to where we are
18 today with respect to the focus being on vasculitis
19 and myocardial injury. Next slide.

20 It came forward to the NCSS, I think it
21 was December 1999 and then again about a year ago from
22 today and I'm going to give you a summary of that.
23 This is essentially overheads that I used for those
24 two meetings.

25 In terms of biomarkers of toxicity, the

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1 general hypothesis is that there exist a more optimal
2 panel of toxicity biomarkers in biofluids and that we
3 can easily access, be it plasma, urine, or circulating
4 leukocytes that can act as sentinels, that we're not
5 presently incorporating into our studies, either
6 routinely and sometimes maybe not even as special end
7 points that could be used.

8 These panels of biomarkers are measurable,
9 can reliably herald the onset of drug-induced system
10 specific damage prior to visible morbidity or
11 significant irreversible insidious damage. So that's
12 the overall hypothesis, that these things exist and
13 we're maybe not using them optimally at the present
14 time. Next.

15 So why do we feel this? What are some of
16 the indications that more and better biomarkers
17 linking exposure to toxicity are needed? Well,
18 overall in general, biomarkers of toxicity haven't
19 changed much in the last 40 years. We're still using
20 a lot of the same biomarkers, or clinical end points,
21 that we've been using for the last 40 years.

22 There is obviously attrition of
23 pharmaceuticals from clinical phases of development.
24 We can't always say that that's because there were
25 biomarkers in the animal that we didn't have and

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1 didn't have to go into the clinic, but to some extent
2 I think we can point to that as a possible reason.

3 Number of drugs, approved drugs, have been
4 removed from the marketplace. Again, maybe
5 biomarkers, improved biomarkers are not the answer to
6 all those, but I think it's quite possible that if we
7 had better sets of biomarkers we'd have a better
8 handle and these kinds of things would happen less
9 often.

10 There's quite often a questioned relevance
11 of certain animal findings for nonclinical studies.
12 What's the relevance to man? So the ability to go
13 into the clinic and extrapolate from species to
14 species remains a gnawing issue at times.

15 There are perceptions of inconsistency
16 across drug review divisions. Some review divisions
17 maybe being accused of being more conservative than
18 others. And possibly it's because the science just
19 isn't there. We don't have the biomarkers to answer
20 some of these issues. Often, not often, occasionally,
21 drugs are placed on clinical hold and oftentimes
22 that's because we just don't have those biomarkers to
23 tell us again whether these animal findings are
24 relevant. And that addresses the last point,
25 questioned relevance of certain animal models as well.

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1 Next.

2 So in terms of using biomarkers of
3 toxicity, accessible, system specific biomarkers of
4 toxicity research in that area, the objective would be
5 to define biomarkers with an improved ability to
6 profile a prioritized set of system specific damage
7 endpoints covering a variety of mechanisms and
8 different drug classes.

9 The goal we might establish is to
10 establish again a more optimal set of these easily
11 accessible biomarkers, to allow us to progress with
12 greater confidence from animal studies into, and
13 through the clinic, to herald early onset of
14 toxicities prior to morbidity and irreversible damage.

15 In terms of general considerations as we
16 approach these issues, we need to focus on biomarkers
17 that are mechanistically related to the pathogenesis
18 of insidious toxicities. We don't want correlative,
19 we want things that are mechanistically linked.

20 We need to choose toxicity of interest to
21 both regulators and sponsors to encourage partnering,
22 and a lot of why we're here today, is I think we've
23 succeeded in identifying a couple of areas that are
24 really of shared concern.

25 We need to choose practical biomarker

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1 strategy that will allow this extrapolation across
2 from animals into man. I guess I've made that point
3 a few times haven't I.

4 Okay, in terms of where we can gain, where
5 we can access these biomarkers, I think we have to
6 keep a very open mind. But they need to be
7 accessible. We have to keep in mind that we can do a
8 lot of things in animals that we can't do in people.
9 We can't pull out lungs and we can't pull out livers
10 and things like that that we can do in animal studies.

11 So we need to those sort of goal endpoints
12 of histopathology that we see in animal studies and be
13 able to extrapolate what's going on in accessible
14 tissues, circulating blood elements. Can we look at
15 cellular RNA? Can we look at proteins that are
16 expressed on the surface? Can we look at alterations
17 in DNA?

18 Accessible clinical biopsies, if they're
19 easily accessible, things like skin.

20 Serum components, be they unregulated
21 secreted proteins, lipid products, steroids. Again,
22 we need to keep an open mind what to look at.

23 Tissue specific proteins that might be
24 released when membrane integrity of a specific organ
25 of interest is compromised.

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1 And then components of other body fluids,
2 like cerebral spinal fluid, like urine, saliva.
3 Again, we need to keep an open mind. Next slide.

4 Now in terms of the evaluation of
5 biomarkers, and getting into a lot more detail but
6 just in terms of the kinds of challenges that we have
7 ahead of us, there are a number of phases that we need
8 to take into mind. The clinical chemistry phase. Is
9 the assay accurate? Is it precise? Is it robust? Is
10 it reproducible? What's the sensitivity specificity
11 and dynamic range of the particular clinical
12 chemistry, just the assay itself.

13 Then as you move into the nonclinical
14 phase of the development and the evaluation, you need
15 to look at things like dose-response, the
16 identification of the action threshold, at what point
17 does this increase mean that you've gotten into a
18 point of morbidity, at least in the animal study you
19 can establish that.

20 Establish the cause-effect relationship.
21 Again, not correlative but actually in the line of the
22 cause-effect relationship mechanistically. Is it
23 sensitive? Is it specific? Is it predictive? Again,
24 there sensitivity, we're talking about drugs, better
25 known to cause the toxicity versus drugs that are know

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1 not to cause the toxicity. We have to make sure we
2 can pick up the sensitive but it's not non-specific.

3 And, again, issues of the relationship
4 between the biomarkers and whether it's telling us
5 anything about whether we're still in a reversible
6 phase or have we crossed into a state of
7 irreversibility. So there's a lot of challenges
8 there.

9 And then, obviously, we've got to come up
10 with a strategy of how we're going to show that these
11 things are clinically relevant, and we have to confirm
12 that aspect of things. So there's a lot ahead of us.

13 So, again, back in March last year, being
14 the good bureaucrat that I am, I wanted to make sure
15 that these weren't just personal ideas, that we had
16 sort of a consensus from our center. And we have a
17 research subcommittee to the Pharm Tox coordinating
18 committee and we posed these issues, you know, in
19 terms of toxicities that we see, that are recurring
20 that we still wrestle with, if we could develop a
21 better panel of biomarkers that would help us as we
22 move into the clinic, to establish better monitoring
23 strategies, what would they be? Where are the sort of
24 priority areas?

25 And I'm going to give you that feedback.

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1 I have it broken up into three tiers.

2 In Tier 1, priority. They felt, again,
3 cardiac toxicity, myocardial injury as I have in (a),
4 but also the issue was raised about the whole QT
5 issue, drugs that prolong QT. There is a parallel
6 effort going on to deal with that so it was felt that
7 for this committee, the myocardial injury would be
8 more appropriate.

9 Vasculitis. Again, the need for
10 biomarkers was endorsed there and the committee
11 encouraged, maybe not even just focusing on
12 vasculitis, but as we look into that area, look into
13 biomarkers of a general immune system activation, keep
14 that window open. Next.

15 The Tier 2 and Tier 3 advice that came
16 from the subcommittee was we still wrestle with issues
17 relating to neurotoxicity. Peripheral damage,
18 neurotoxic damage, are there plasma markers that can
19 reflect that? Central damage, are there again serum
20 markers or CFS markers we could use? Non-invasive
21 imaging, again Jim already related to that, so that is
22 sort of on the table in that other effort.

23 Hepatotoxicity, the feeling was to wait and
24 not bring to the NCSS at this point. The FDA/PhRMA
25 conference which was just held just held a short time

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1 ago, I can't remember which month it was. But there
2 was some advice coming from that, and there will
3 probably be some efforts as a result of that as well.
4 But, as of March of last year, the thing was to wait
5 for that, and that is something that either the NCSS
6 or some other parallel structure will probably work
7 toward biomarkers to better predict and diagnose
8 hepatotoxicity. Next.

9 And the third tier, things are sort of in
10 the wings. Photocarcinogenicity, we have animal
11 models, there's a general feeling that we would also
12 like to have biomarkers, and here again maybe skin is
13 a possible place to look for biomarkers of whether we
14 have a relevant human photocarcinogen.

15 And renal toxicity. There is an ongoing
16 ILSI initiative focused primarily on genomics, but
17 samples are being saved from those studies and
18 proteomics for looking at biomarkers is a possible
19 spin-off there. So that could be coordinated with
20 that initiative and ILSI is looking for ways to move
21 forward.

22 There's also an NMR consortium working
23 through the Imperial College and I believe a number of
24 the members in the audience today are a part of that
25 consortium as well. So these things are going on.

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1 But we felt that vasculitis and myocardial injury
2 really deserved some attention that wasn't being met
3 elsewhere. Next.

4 So just in terms of giving you a feel for
5 some of the kinds of issues that are out there and,
6 again, I'm preaching to the choir a little bit here
7 because I know some of our members have wrestled with
8 these issues firsthand, trying to develop drugs that
9 have caused vascular injury in their nonclinical
10 studies.

11 This is an example that was published,
12 this was presented at SOT a couple of years ago. This
13 was a drug, PDI 747, that was developed by Novartis.
14 It's a phosphodiesterase type 4 inhibitor being
15 developed for inflammatory skin diseases.

16 As you can see, they found positive
17 vasculitis findings after just two weeks and 13 weeks
18 in the GI tract and also myocardial necrosis was seen.

19 In terms of a safety margin, the doses
20 they want to get to in the clinic were going to be 25-
21 fold higher than the doses that were causing the
22 toxicity in the rat.

23 The dog, they also saw vasculitis and
24 myocardial necrosis, myocarditis. There, the doses
25 they wanted to get to in the clinic would have been

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1 50-fold higher than the doses that were achieving this
2 toxicity in the dog.

3 The mouse was listed as positive, the
4 minipig was also positive in the mesenteric; the
5 monkey was also listed as positive, I don't know the
6 information in terms of the site of predilection. In
7 the rat, it was also listed as a positive.

8 So every single species they looked at it
9 was positive. One could still ask the question, is it
10 going to incur in humans? And we may never know. But
11 they felt that it would not be wise to develop that
12 compound at this point in time. Next slide.

13 Here's something that's maybe a little bit
14 tougher and we have a company Y that's developing a
15 drug X and mesenteric vasculitis and death is seen in
16 the rat study. The company is not seeing clinical
17 efficacy in their phase 2 trial and they want to
18 increase the dose. They want to increase the dose to
19 either meet or exceed the AUC that was in the rat that
20 was shown to cause mesenteric vasculitis. So you have
21 an impasse, and largely because there's no clinical
22 biomarker to monitor for these findings in the clinic.

23 The histopath clearly shows early injury
24 to rat vascular endothelial and smooth muscle cells,
25 and what we have done is we've initiated proteomics

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1 approach in our laboratories and we have a number of
2 collaborations going with people to try to address
3 this kind of issue. But this is not atypical, the
4 kinds of things that have been seen in submissions and
5 it cuts across class. Some phosphodiesterase
6 inhibitors, some will be endothelial recipient -- some
7 will be reverse transcriptase inhibitors. There's a
8 number of different classes. Some basoactive, some
9 not so obviously basoactive compounds for which
10 vasculitis findings were seen. Next slide.

11 In terms of switching over to myocardial
12 injury, there we're a little more advanced in our
13 tools that we have available to us. So myocardial
14 injury biomarkers do exist, we have isoforms of -- we
15 have isoforms of LDH that we can monitor, and these
16 have been shown to reflect acute myocardial injury as
17 a result of myocardial infarction, for example.

18 When it comes to monitoring for drug
19 induced cardiac toxicity, we have evidence that
20 Troponin T may be even more promising biomarker of
21 drug induced cardiotoxicity, both acute and chronic.
22 Here, I'm just showing a representative example of
23 some of the data that's come out of Gene Herman's lab
24 in my division, showing Troponin T increasing as
25 weekly doses of DXR, and one milligram per kilogram

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1 are given to a rat model that he's developed over the
2 years, showing a nice increase with time and Troponin
3 T. What I haven't shown you is that the myocardial
4 injury histopath also reflects very nicely the
5 increase that's seen in Troponin T.

6 Now Gene has developed data not just
7 showing this, but looking at differential sensitivity
8 between males and females. Again, the correlation is
9 very good between histopath and the biomarker, cardio
10 protectin, pre-administration of cardio protectin
11 reflects again that Troponin T is working as a nice
12 predictor, that is inhibited by the cardio protectin
13 as is the histopathology. He's done other classes of
14 drugs on both acute myocardial injuries and as chronic
15 and it's looking quite promising.

16 So the question is with this particular
17 approach, with this particular question, is what do we
18 need to do to get this into routine practice in terms
19 of the drug developers? With vasculitis, there's a
20 wide open field. We don't really have anything at the
21 present time. But with myocardial injury we have a
22 few candidates and we feel that we have a better one
23 than the ones that can be measured sort of routinely,
24 but we sense a reluctance on the part of the industry,
25 citing reasons for not using it. So what we do we

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1 have to do collectively?

2 And there are other ones. There's
3 Troponin I, there's Troponin T, there are biomarkers
4 of response, hypertrophic response that we'd be able
5 to like to use on non-invasive. So there are other
6 things there.

7 What do we need to do collectively to get
8 these into practice? Next slide.

9 These are some of the thoughts. Again,
10 sensitivity/specificity. How many different drugs do
11 we have to look at that are known myocardial injurers.

12 How many drugs we have to look at that are
13 known not to injure the myocardium, but maybe injure
14 the kidney and not the myocardium. Do we see a
15 Troponin T increase? So that we can at least know how
16 predictive and what are the limitations of Troponin T
17 if we choose that as something that we want to look
18 at. What's the robustness, reproducibility, dynamic
19 range, the half life of the biomarker? These are very
20 practical questions that we need to address. Related
21 dose exposure and time, as we choose the agents that
22 we want to test.

23 Then look across species, across different
24 strains, across gender variations and relate to the
25 "gold standard" histopath observations. This is sort

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1 of a primitive strategy that I put there that would
2 probably need to be applied. Next.

3 So the question that was posed to the NCSS
4 back in December of 1999 and again in March of 2000,
5 was who should assume the costs of biomarker
6 identification and evaluation? Is this an FDA
7 responsibility? Is it NCTR responsibility? Is it
8 CTER responsibility? Is it Pfizer's responsibility?
9 Is it Lilly's responsibility? How do we start, how
10 do we prioritize. Is it the academic's world
11 responsibility?

12 Well the vision that we shared with the
13 NCSS and the NCSS picked up on was that this should be
14 a collaborative effort to define improved panels of
15 biomarkers for specific toxicities that cut across
16 species and built into a very practical format that's
17 easily implemented. Next, and I think my last.

18 So the impact of achieving this vision
19 will be to assess the relevance, or irrelevance, of
20 animal toxicity findings, to accurately assess doses
21 that are associated with toxicity. To maximize a
22 favorable impact on public health. To minimize
23 regulatory dilemmas impasses. To improve selection of
24 candidates for drug development and reduce candidate
25 attrition rates. To accelerate drug development,

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1 minimize resource consumption and make for a more
2 perfect world.

3 I think that's the last slide. Is that my
4 last slide? Yes. Okay. Thanks. Any questions? Do
5 I take questions now?

6 CHAIRPERSON DOULL: Sure, why don't you,
7 Frank.

8 DR, SISTARE: Okay.

9 CHAIRPERSON DOULL: Questions for Dr.
10 Sistare? A more perfect world.

11 Well, you've heard from Helen and Jim how
12 all this got started and how we have all ended up here
13 together, and you've heard from Dr. Sistare about why
14 we selected cardiotoxicity and vasculitis as the two
15 working groups to start off with.

16 This is a novel, a new approach for Food
17 and Drug and it's as you can tell I'm sure from
18 listening to these presentations, it's been difficult
19 to do this. We had all sorts of ideas initially about
20 how this would happen. We thought, for example, a
21 subcommittee would appoint the working groups; it
22 turns out officially we can't do that so the
23 subcommittee gave input to Food and Drug so you were
24 actually appointed by Food and Drug.

25 We thought it would happen very quickly.

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1 As you can see, it's taken quite a while. But it's
2 very important because this sets a pattern, in a
3 sense, what has been accomplished by forming these
4 groups, emphasizes something Food and Drug has said
5 for a long time, we want to do cooperative things with
6 industry and with academia that benefit us all in the
7 development of new drugs and in the testing of drugs.

8 We need a mechanism that makes this work,
9 and this is an opportunity for us to demonstrate that
10 there is a mechanism, that it can be used, and that in
11 fact it does hopefully will work. That's really what
12 we'd like to demonstrate.

13 I might also say in regard to the -- our
14 subcommittee has two goals, one is a scientific goal
15 and you've heard about that, we want to find
16 biomarkers that are more predictive than what we now
17 have. Those biomarkers actually could be very helpful
18 in the development of new drugs. They could be very
19 helpful in pre-clinical testing of drugs that have
20 come along that far.

21 We heard the speaker talk about the
22 possible use of biomarkers to identify people who have
23 a genetic fault, or for some reason or other are more
24 susceptible to that particular drug and some examples
25 for that. So there are lots of scientific

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1 opportunities for us to work together to develop
2 biomarkers so they're more useful.

3 And the other aspect, which I've already
4 mentioned, is of course the collaborative one. It's
5 very important I think that we figure out how to get
6 around the difficulties and make a collaborative
7 effort of this nature work.

8 I might just say a word about Dr.
9 Sistare's presentation. The subcommittee, as he
10 indicated, has met several times and we've looked at
11 a lot of different areas that we could get into and
12 form working groups and so on. And he showed you
13 several of those, a neurotox for example. The
14 subcommittee talked a great deal about genomics and
15 proteomics and other "omics" and the need for a
16 working group in that area. We're all very excited
17 about that and think it has great potential in
18 toxicology as well as development of drugs.

19 But our subcommittee did not really feel
20 we were at the stage where a working group would
21 really be very profitable in the "omics" groups, and
22 we do have very good links, courses, the leader of
23 that group for NIEHS and Dan, of course, is aware of
24 what's going on at NCTR. So as soon as that gets to
25 a stage where it would be useful to have a working

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1 group, hopefully the subcommittee will be able to do
2 something in a way that would be helpful.

3 Another area that Jim mentioned is the
4 non-invasive, the imaging techniques, and we've had
5 some beautiful presentations on PET scan, for example,
6 and NMR and how they can be used as biomarkers to
7 locate drugs and to look at distribution and so on.
8 And those are also very exciting developments.

9 PET scanning is very expensive, there
10 aren't a lot of machines out, and it kind of is at the
11 stage where it's a demonstration technique. It really
12 does some things very elegantly, but the subcommittee
13 felt after a lot of discussion, although we initially
14 recommended that maybe we should have a working group
15 to do PET scanning, that we probably weren't quite
16 ready to get into that. There wasn't enough mass out
17 there to make that a go situation and also for NCTR or
18 for NMR.

19 We talked also about kinetics at some
20 length. I think there was a lot of enthusiasm amongst
21 members of the committee for a kinetics area,
22 pharmacokinetics, pharmacodynamics, pharmacokinetics,
23 the modeling sort of techniques. But the ones that we
24 selected, I think, represent what the agency and what
25 this committee felt were the most likely ones to give

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1 us some bang for the buck.

2 In thinking about this, I've gone back and
3 looked at definitions for biomarkers. It's
4 interesting that that term does not go back a long
5 ways. If you look in medical dictionaries, for
6 example, some time ago you don't find biomonitoring or
7 biomarkers and so on. It's a relatively new term.
8 And so I looked for a definition, and I found the
9 Academy has a definition which they used in 1989 but
10 Elaine Kaufmann and her committee on developmental
11 toxicology just recently restated that definition.

12 I think because of the fact that we're
13 dealing in a whole bunch of different areas, imaging,
14 genomics and what have you, we need to have some
15 concept about what biomarkers really, you know, what
16 we mean by that term. And let me just read the
17 Academy definition.

18 Indicators, signaling events in biological
19 systems or samples. There are three classes of
20 biomarkers; biomarkers of exposure, biomarkers of
21 effect and biomarkers of susceptibility. A marker of
22 exposure is an exogenous substance or its metabolite,
23 or the product of an interaction between a xenobiotic
24 agent and some target molecules or cell that is
25 measured in a compartment within a organism. A marker

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1 of effect, which would be more like what we're
2 concerned with in cardiotoxicity and vasculitis, is a
3 measurable biochemical, physiological or other
4 alteration within an organism that depending on
5 magnitude can be recognized as an established or
6 potential health impairment or disease. And a marker
7 of susceptibility is an indicator of the inherent or
8 acquired limitation of an organism's ability to
9 respond to the challenge of exposure to the specific
10 xenobiotic substance.

11 Like most Academy definitions, they're
12 pretty wordy, but I think one of the things that your
13 groups could do would be to think about how we define
14 biomonitoring and biomarkers in a way that's broad
15 enough, for example, to encompass what it is we really
16 need to talk about.

17 Regine Henderson, a couple of years ago
18 she had an article in Critical Reviews in Toxicology
19 and she pointed out that we need to think about
20 biomarkers not as a process or a test or something,
21 but as a piece of information, and that that is really
22 how we're using it, as a piece of information which
23 has high predictivity for whatever it is we want to
24 know.

25 The CTECH people talked about biomarkers

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1 and it was interesting because they talked about so-
2 called gold biomarkers. Those are ones which are
3 highly specific and the example they used was
4 cholinesterase, for example. Cholinesterase is
5 inhibited by OPs or whatever, but that's a gold
6 biomarker in that it's very specific for a chemical.
7 ALA would be the same thing for lead, for example.
8 Things that are really compound specific and in that
9 sense are what they would call a gold biomarker.

10 They talked about silver biomarkers and
11 there they're talking about things like DNA adducts,
12 which are generally less specific than like, say,
13 cholinesterase. And for bronze biomarkers, the lowest
14 category, they talked about things like P450, zip one
15 and zip two, which occurred with a whole bunch of
16 different enzyme changes in general.

17 So that's something also you might think
18 about is the usefulness, or the quality of the
19 biomarker if that's a useful kind of thing that you
20 all might get into.

21 We have not in this process defined
22 exactly a task. In the Academy, for example, it's
23 customary when we form a new committee that we give
24 them a statement of task. But on the back sheet of
25 this background material, background document, there

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1 is a page of proposed objectives which are
2 specifically for this committee. You all may need to
3 look at those, you may need to modify them, but those
4 were some of the ideas that we thought might serve as
5 a working recommendation.

6 And let me just quickly go through those.
7 First, to identify the areas of science which are of
8 common interest to both FDA and the stakeholders so
9 that they may collaborate effectively to advance
10 methods and techniques by which to identify and
11 prevent drug induced cardiotoxicity and vasculitis,
12 which focuses on that collaboration which is clearly
13 one of the major goals.

14 Second, to define specific objectives
15 within the fields of cardiotoxicity and vasculitis
16 that could be achieved by collaboration, and also to
17 identify resources, effort and the time required to
18 achieve specific milestone determined by each group.

19 Third, to identify potential collaborators
20 who have resources and interest in achieving these
21 objectives.

22 Fourth, to identify mechanisms by which a
23 collaboration could be effected, and I would add
24 enhanced.

25 And, fifth, to define benefits to be

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1 realized by agreeing upon these objectives.

2 Those are very general but are kind of
3 guidelines, if you will, that the NCCS would like to
4 give you all to start off this task.

5 Let me ask other committee members for
6 comments.

7 MEMBER GOODMAN: I think one thing that's
8 also important to consider is overall philosophically
9 to not just look to add new tests, but to see if
10 anything that is currently being done maybe can be
11 eliminated and done better, as opposed to just simply
12 adding to the list of tests.

13 CHAIRPERSON DOULL: Jay is speaking from
14 experience. A couple of weeks ago, several of us were
15 at a meeting, an ILSI meeting, to see if we couldn't
16 simplify the testing. It happened to be for
17 pesticides, but the toxicity arguments are applicable
18 across the board.

19 Old tox tests are like old soldiers --
20 they just never go away. They just keep on and on,
21 and we add each time. We need a system whereby we can
22 look at what we do and say is that really the best way
23 to determine whether this material is going to have an
24 adverse effect in the public. We don't do them any
25 great service by simply adding a whole bunch of new

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1 tests.

2 CHAIRPERSON DOULL: Other comments? Joy?

3 MEMBER CAVAGNARO: Just one comment and I
4 note that we have representatives from companies and
5 perhaps international flavor, and I think that, you
6 know, as we move forward since this we're in a global
7 environment now, that I think it's going to be
8 important to see how this impacts actually globally.
9 If there are recommendations from this committee and
10 how not only do we move forward and to try to get
11 acceptability, as Frank said, in terms of development
12 programs, but a consideration about how we move
13 forward in a global setting I think is going to be
14 pretty important as well.

15 MEMBER ANDERSON: I would like for you to
16 comment on the objectives which you just did from the
17 background paper, and the role and objectives here.
18 How these two relate. This is very general and this
19 one was very specific..

20 CHAIRPERSON DOULL: Okay. Gloria -- Dr.
21 Anderson -- is talking about the objectives, Jim, that
22 you had in your slides which are somewhat different
23 than the ones that are at the end of the backgrounder.

24 DR. MACGREGOR: Okay. I think that what
25 I'm trying to lay out is, in a way, a parallel to the

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1 objectives that John just read. You're referring to
2 the ones that I presented versus the one that was in
3 the backgrounder that John just read.

4 And I think actually they're not
5 incompatible and mine is just, as Dave just said,
6 really a checklist of things that need to happen
7 today, and that the groups need to address. I think
8 that's what I was intending to lay out in a general
9 sense. The overall thing we want to get out of these
10 groups, and the subcommittee, are the objectives that
11 John just read.

12 MEMBER ANDERSON: I was concerned, and I
13 guess you've answered it, that these are very general
14 so I guess this would be general down to the specific
15 ones, so this will not supercede the specific one that
16 you have here. Is that correct?

17 DR. MACGREGOR: Yes, I think that's
18 correct. And in a sense, I guess, in my mind
19 personally as a personal comment is that both of these
20 sets are fairly general. That is that I think that
21 the subcommittee has come to the point of considering
22 information and case histories and been convinced that
23 these are important areas in which progress could be
24 made, but that the subcommittee did not really possess
25 in depth expertise in these technical areas. So these

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1 are purposely left general enough that when we bring
2 together these experts that we now have, that they
3 would have the latitude to put forward their views on
4 really what are the best opportunities and either
5 confirm our thoughts or extend them, or come up with
6 a better set.

7 CHAIRPERSON DOULL: We could, in fact, get
8 a recommendation from you guys that we ought not to be
9 doing this, that it's premature or that there isn't
10 enough information out there, whatever. And that
11 certainly is an acceptable recommendation. We've made
12 our best guess as to where the possibility for some
13 good recommendations might come forth but, you know,
14 we rely on you to tell us whether that was a wise
15 recommendation and how to implement it.

16 I'm sure over the period of time we're
17 going to have a lot of concerns about the mechanism of
18 all this. How we get the meetings. You've already
19 heard about do we have to have it in the Federal
20 Register. Well, we don't have to do that. But we
21 will need to deal with the mechanics of all this, how
22 we arrange to keep track of what you're doing and
23 whether you want to have meetings with this committee
24 or how we keep in communication and so on.

25 We intend to be fairly active in following

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1 along what you're doing because it's important to us
2 and it's important to the Food and Drug.

3 So do you all have any questions for the
4 committee?

5 DR. MACGREGOR: Yes.

6 DR. ROSENBLUM: Is it working? I was
7 curious about another activity that's ongoing, it's an
8 ILSI sponsored, I think it's called nonclinical
9 clinical toxicity correlations, and that's been
10 meeting for a couple of years now.

11 It seems to me that the progress of that
12 committee could significantly impact the objectives of
13 this committee, and I was wondering was there any
14 attempt to bring those two functions together or to
15 correlate them somehow?

16 DR. MACGREGOR: Yes. Could you give your
17 name for the --

18 DR. ROSENBLUM: Oh, I'm sorry. Rosenblum,
19 Schering-Plough. Sorry about that.

20 DR. MACGREGOR: We had at our, I forget
21 which meeting, Denise Robinson from ILSI to come and
22 talk about some of the ILSI activities. We are trying
23 not to reinvent the wheel. ILSI, for example, has a
24 big liver ongoing activity and, as Frank mentioned,
25 that's one area that we have avoided somewhat.

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1 I'm not familiar specifically with the one
2 you're talking about.

3 DR. ROSENBLUM: Could I just extend that.
4 What was particularly of interest to me was that the
5 ILSI committee activities were attempting to get at
6 predictivity of toxic findings in animal models as it
7 relates to human safety, and it seems to me that
8 that's very germane to what we're trying to accomplish
9 here.

10 DR. MAGREGOR: I agree.

11 DR. DEGEORGE: I'm Joseph DeGeorge. The
12 ILSI effort though is a slightly different effort.
13 It's actually designed to look at -- the current
14 effort is designed to look at the pharmaceuticals in
15 development now, what findings are observed in animals
16 and whether or not those findings are then observed in
17 the clinic, if in fact it comes to fruition. That's
18 a little different than trying to identify improved
19 better biomarkers, for example for cardiac toxicity,
20 that might be more predictive of the outcome in the
21 clinic, over whether you are getting any changes in
22 the clinic at therapeutic doses that might be
23 predictive that if you went higher, you would see a
24 cardiac toxicity, for example.

25 I mean the ILSI effort won't be able to

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1 tell us whether the model is predictive, other than
2 the fact that you observe cardiac toxicity in the
3 animals at some dose level, and at some other dose
4 level you do not yet observe cardiac toxicity. The
5 biomarkers might actually improve that prediction by
6 allowing you to extend and say, well, if you double
7 the dose clinically, which you don't have to do, you
8 would in fact see the cardiotoxicity or some early
9 signs of it in humans.

10 So they're somewhat, they're parallel to
11 both important efforts but this takes on a different
12 focus. In fact, I think the topics that were chosen
13 as areas were also areas where it was felt from the
14 original ILSI effort that there was very little
15 predictivity, given our current techniques.

16 CHAIRPERSON DOULL: Thank you, Joe. You
17 know, that's something that if it would be helpful
18 certainly we could facilitate, you know, communicating
19 that information either through Food and Drug people
20 on that committee or through ILSI itself. If that's
21 something that would be helpful to you all. Yes?

22 DR. MACGREGOR: I was just going to
23 comment. I think the point is well taken that there
24 in fact are a number of different collaborative
25 activities that are going on that these groups need to

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1 pay attention to and try to coordinate with that.

2 As John pointed out, we did have Denise
3 Robinson and also Gwyn Morgan, who was at the time
4 chairing the genomics initiative in the ILSI
5 consortium, come and talk about those activities.
6 And, in fact, those types of activities were
7 considered when we chose the initial two general
8 topics and, in particular, when we went to the theme
9 of accessible biomarkers, because there are a number
10 of different groups that are using genomics, i.e. gene
11 expression chip approaches, which is really in some of
12 our minds, I would say in my mind, more of a, it's a
13 useful tool in discovery and it's kind of a discovery
14 tool for clinical and accessible nonclinical
15 biomarkers.

16 But in general your nucleic acids are not
17 accessible and because there really wasn't a
18 consortium that was approaching the accessible
19 markers, which when identified could be immediately
20 brought into use. That was part of our thinking in
21 going to the accessible marker theme to try to focus
22 there for those two reasons because there were things
23 going on and also because by approaching the
24 accessible markers you'd have things that would be a
25 little faster to bring into practical application.

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1 DR. ESSAYAN: There's another issue that
2 has been raised by some of the comments here, and
3 that's that there are sort of two levels of
4 approaching this problem. There's the discovery level
5 and then there's the validation level. I think one of
6 the things that this committee is interested in
7 looking at is not just the identification of the
8 biomarkers but the ability to validate them in a way
9 that will be useful.

10 The validation part as a regulator becomes
11 a very central point in what we need to do here.
12 Identification can be done prospectively but there may
13 need to be some retrospective data collected in the
14 circumstance where we know a toxicity occurred to look
15 at whether we can validate the preclinical homologue
16 and the clinical data that can be acquired. And then
17 potentially raising that to the next higher level of
18 structure function homology and whether we can detect
19 classes, or structures, that may then predispose to
20 these adverse events.

21 CHAIRPERSON DOULL: It occurs to me we
22 should, we can get a copy of your slides to the
23 committee and some of the material from the August
24 meeting might be helpful also. I'm just thinking of
25 things that we have talked about, for example, that

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1 might be helpful to you all. We can certainly
2 facilitate that. Yes?

3 DR. ROSENBLUM: Frank nicely pointed out
4 some of the progress on the Triponin T as a potential
5 biomarker. I would like to ask Frank is it
6 appropriate to review some of the progress on the so-
7 called genomics front, i.e. microarray work that's
8 been conducted over the past many months. And, in
9 fact, I think Frank you yourself have looked at
10 doxorubicin in terms of gene expression analysis.

11 I'm just looking for sort of updates on
12 some of the newer technologies that are not yet in
13 published journals but data is floating around.

14 DR. MACGREGOR: Yes, Rosy, you're hitting
15 a big question and I'm not sure exactly how we're
16 actually going to do that. All of us have data that
17 we have that would be very good to share amongst
18 ourselves in terms of our own experiences. I know
19 Roger Brown at Glaxo has done some really nice stuff
20 with doxorubicin and looking at -- leucocyte gene
21 expression changes, for example. We have to figure
22 out how we're going to do that in some sort of a
23 systematic way. I don't know the answer to that.

24 I just touched on and very briefly talked
25 about some of the experiments that we had done and

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1 just gave you the one slide. You know, we could spend
2 hours probably going over all the details of what we
3 did and I don't know how we're going to do that in the
4 expert working groups. We do need to sort of,
5 everybody needs to share what they're doing, where
6 they are, how they're doing what they're doing, who
7 they're working with. That's a big question.

8 CHAIRPERSON DOULL: It's a lot easier to
9 deal with a working group than it is with a
10 subcommittee.

11 DR. SISTARE: And I think that's an
12 appropriate question for the expert groups to address.

13 DR. JOHNSON: I have a separate but
14 related question. Dr. Sistare, you mention I believe
15 that the QTC prolongation is going to be covered in a
16 parallel effort. Can you qualify that? And I guess
17 in sort of a related way, is the cardiotox group
18 expected to address that specific issue?

19 CHAIRPERSON DOULL: Identify yourself for
20 the record, please.

21 DR. JOHNSON: Oh, I'm sorry. Robert
22 Johnson, Schering-Plough.

23 DR. DEGEORGE: Again there are actually --
24 Joseph DeGeorge, FDA. There is an industry and FDA
25 effort, actually there's an international effort

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1 ongoing look at evaluating appropriate test systems
2 for QT sorts of efforts. In fact, the industry is
3 testing a number of pharmaceuticals that they've
4 picked out with both positive and negative outcomes in
5 humans to derive appropriate animal models to address
6 that.

7 I think it was felt by at least the
8 Pharmtox coordinating committee's research
9 subcommittee that that effort was being addressed, and
10 to have another group try to do the same thing would
11 not really facilitate getting to an answer. Again,
12 industry's already investing a significant amount of
13 research effort into that. The FDA is working with
14 them on that effort within CDER. Internationally
15 there's an effort underway under the ICH to generate
16 an evaluation of current methods. So there's already
17 a lot of activity on that. The direct cardiotoxicity
18 effort is one which no one seems to have picked up and
19 which we clinically run into problems with and
20 nonclinically run into problems with. So trying to
21 get an effort there was thought to be a better use of
22 limited resources.

23 DR. JOHNSON: What was the formal name
24 though of that group?

25 DR. DEGEORGE: The formal name I am not

1 sure, but it's part of the subcommittee that is doing
2 that under the safety pharmacology group.

3 CHAIRPERSON DOULL: Other questions?
4 Concerns?

5 DR. SISTARE: Let me make one thing clear
6 though. That list that I gave you is like a Tier 1,
7 Tier 2, Tier 3, those were the recommendations that
8 were brought from a research subcommittee that's part
9 of the Pharmtox coordinating committee which Joe is
10 the policy head on that. So those were the
11 recommendations that I brought forward to the NCSS,
12 then the NCSS from this banquet or, you know, from
13 this plate of possibilities, they agreed that the Tier
14 1, those two were the most appropriate. And, because
15 of the parallel effort that Joe talked about, let's
16 not deal with QT in this group. Let's focus on
17 biomarkers of myocardial injury and possibly response
18 to injury with time.

19 So the cardiotox group is not to focus on
20 rhythm issues.

21 CHAIRPERSON DOULL: But that's not a
22 restraint. If you guys feel that you need to look at
23 that or talk about it or consider it, then obviously
24 you know whatever makes it work.

25 We are extremely anxious for it to work

1 with these two committees because we have a lot more
2 possible advisory committees that we're thinking about
3 down the road, and that we would like this to be a
4 model to help us make them all work. Yes, sir?

5 DR. ROSENBLUM: Well, insofar as many
6 cardiotoxic drugs are toxic by virtue of functional
7 changes and not necessarily structural changes, I
8 don't see how you can separate the two areas really.

9 DR. SISTARE: Well, you could ask the
10 question and it would be a fair question. If you have
11 a drug which causes a rhythm disturbance, will you be
12 able to monitor that by looking at some -- biomarker?
13 I mean I'm open minded, you know, that's possible.
14 I'm not suggesting that may be the best way to pick it
15 up, but it's quite possible.

16 But, again, the focus was on, you know,
17 compromising the integrity of the myocardial injury
18 per se. You know, it may be that these things with
19 continued injury may result in fibrosis that
20 ultimately does result in a rhythm disturbance or
21 electrical disturbance. You know, these are great
22 questions to bring up and you shouldn't throw anything
23 out, at least in the early part.

24 DR. HOLT: Gordon Holt. In playing off of
25 what Frank suggested about the value of being able to

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1 share data, an obvious impediment to that is
2 confidentiality. And I know that my company certainly
3 has a lot of contractual obligations that certainly
4 would complicate sharing of data.

5 I wondered if it's possible, I appreciate
6 that this forum can't be under CDA, I wondered if
7 there's a possibility of taking some segment to the
8 working groups into a confidential setting so that we
9 can share actual data and actual experiences.

10 DR. MACGREGOR: Well, Nancy, do you want
11 to comment on that?

12 DR. CHAMBERLIN: We have a transcriber for
13 the morning session and that's being videoed. We were
14 trying to do the working task force in an open session
15 and initially for the first meeting to get the ground
16 rules going, you can do open session. But at some
17 point, if you do want to choose to do confidential
18 information, you can set your ground rules there. But
19 we were trying to be upfront in the public, but in
20 order for say confidentiality, I mean that's your
21 call.

22 DR. HOLT: Should we discuss that in a
23 working group or could I persuade you guys? I feel
24 with great confidence if we polled real quickly here
25 that everybody would say we'll make a lot more

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1 tangible decisions if we can, not for the entire
2 working groups, but just at some point we can say from
3 here on this is confidential information.

4 DR. MACGREGOR: Why don't you take it up
5 in the working groups early on and we can then decide
6 how to proceed.

7 CHAIRPERSON DOULL: Nancy says we have no
8 requests for public comments, but are there any public
9 comments that anybody would like to make, either to
10 the working groups or the subcommittees?

11 Well, I think we know at least where we're
12 at which is not all that well formulated but we've
13 left it loose intentionally because we're not sure how
14 the best way to make it work. And that's what we're
15 going to explore this afternoon.

16 Do you have any other additional details?
17 You've taken care of the administrative things, lunch
18 and so on?

19 DR. MACGREGOR: Yes, I mean my only
20 question would be if we're about to wrap up we can
21 obviously begin working earlier, so we'll just have to
22 think about our logistics since the plan was to have
23 one of the groups go to a remote site. We'll just
24 have to check on our transportation and maybe take a
25 short break and then formulate a plan on that.

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1 CHAIRPERSON DOULL: Yes, why don't we do
2 that. Why don't we just take a ten minute break and
3 we can talk about that and then figure out how best to
4 do our afternoon sessions.

5 (Whereupon, the proceedings went off the
6 record at 10:08 a.m. and resumed at 10:34 a.m.)

7 CHAIRPERSON DOULL: I think we'll start
8 our working group meetings early and Dr. MacGregor is
9 going to fill us in on how we're going to do that.

10 DR. MACGREGOR: Okay. Since we're done,
11 there'll be a slight amendment to the general plan
12 that I announced earlier. We're going to begin the
13 working group meetings right away before lunch so
14 you'll have some time to discuss and get organized
15 before lunch. And because the meeting for the
16 vasculitis group, it's not far away but it's not right
17 here either, I think it's going to be easier not to
18 try to get everyone together for lunch.

19 So what we're going to do is we have
20 arranged for transportation for those of you that are
21 in the vasculitis group to go over to the Ramada Inn.
22 There's a meeting room there, Nancy what is the
23 meeting room number?

24 DR. CHAMBERLIN: I think they changed it
25 to the Georgetown Room. Originally it was the --

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1 DR. MACGREGOR: Georgetown Room, okay. So
2 Georgetown Room at the Ramada Inn. And we have the
3 transportation arranged at approximately 10:45 but we
4 won't leave until we have you all, to bring people
5 over there. So people that are in cardiotox group
6 will stay right here in this room and we'll reconvene
7 in about ten minutes after John closes this meeting.
8 And then at about that same time we'll have
9 transportation for the vasculitis group.

10 Now the transportation will be a van that
11 will hold four people, so the first four of you see
12 Nancy. Nancy, raise your hand. The first four people
13 that see Nancy, she'll just take you out this door
14 right here and there'll be a van. But the people that
15 have cars can't get in that parking lot. So the rest
16 of you go upstairs to the main lobby of this building,
17 and the main lobby faces Fisher's Lane. Go out the
18 main lobby and walk across Fisher's Lane to the other
19 side of the street, because that's where the cars can
20 pull up and there'll be three or four cars of people
21 going over there.

22 So first four go with Nancy, the rest of
23 you in vasculitis go upstairs, across Fisher's Lane
24 and there'll be cars there to bring you over. There
25 are a number of restaurants right adjacent to the

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1 Ramada and Dave Essayan, who's our liaison to the
2 vasculitis group, will make sure you find one of those
3 restaurants and eat. And I'll be staying with the
4 cardiotox group here, and we'll just follow the
5 original plan of going over to the cafeteria.

6 And also a reminder, seven o'clock
7 everyone that would like to come together for lunch,
8 seven o'clock at That's Amore restaurant, which is
9 directly across the street from the Doubletree Hotel,
10 directly across Rockville Pike and in the same parking
11 lot actually with the Ramada. So just ask if you have
12 any confusion, the people at the hotel where is That's
13 Amore, and we'll see you at seven.

14 CHAIRPERSON DOULL: When we introduced the
15 working group members we neglected a couple of the
16 Food and Drug reps. So we'll -- Tom and Elizabeth.

17 DR. MACGREGOR: Yes, an oversight in my
18 introduction that we also in setting up these groups
19 recognize that each of the FDA centers that's involved
20 really ought to have liaison contact with these expert
21 groups. And we gave each of the three centers that
22 are now actively involved, CDER, CBER and NCTR, the
23 opportunity to appoint liaisons to these expert
24 groups.

25 And CDER has appointed one to each group,

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1 Tom Papoian, Tom are you here from CDER, to the
2 vasculitis group and Elizabeth, Liz Hausner to the
3 cardiotoxicity group. So they'll be liaisons to CDER.
4 For the moment I will be functioning as the NCTR
5 liaison to both groups and Dave Essayan the CBER
6 liaison to both groups. And we also have, Dave and
7 myself will be keeping track of the groups as part of
8 our function of being the NCTR and CBER liaisons, FDA
9 liaisons actually with the subcommittee group.

10 CHAIRPERSON DOULL: Okay. One final
11 thing. When you meet in your working groups, why
12 don't we start out with Jim being in charge of the
13 cardiotoxicity one, just to get it organized so you
14 can do your thing. And Dr. Essayan being in charge of
15 the vasculitis one, and he can help you then get it
16 organized.

17 Is there any additional business that
18 needs to come to this committee? Then I would like to
19 thank all of you for being here to day to help us get
20 this business started. Thank you very much. We're
21 adjourned.

22 (Whereupon, the above-entitled matter went
23 off the record at 10:38 a.m.)
24
25

CERTIFICATE

This is to certify that the foregoing transcript in the
matter of: Advisory Committee for Pharmaceutical
 Science, Nonclinical Studies Subcommittee

Before: DHHS/FDA

Date: May 3, 2001

Place: Rockville, MD

represents the full and complete proceedings of the
aforementioned matter, as reported and reduced to
typewriting.



A handwritten signature in black ink, written over a horizontal line. The signature is cursive and appears to be "R. J. [unclear]".

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