

1 | that would be coming up from this subcommittee. But the  
2 | concern was that we not lose those critical links.

3 |           So, I'm going to now kick it back to Helen  
4 | because Helen and I have been talking about how we might  
5 | move to the center that has the resources, use those  
6 | scientific resources for the discussion/recommendation  
7 | development, and still not lose the critical links between  
8 | CDER, the regulatory center, and also to make sure that all  
9 | parties are comfortable that the information channels and  
10 | flows would be maintained. So, I think we have talked  
11 | about solutions that would make them work well.

12 |           Helen?

13 |           MS. WINKLE: Jim, I just have a question before  
14 | I talk. When this was discussed at NCTR, did you talk any  
15 | about actually supporting these projects and whether the  
16 | resources were going to be available? I'm just curious.  
17 | As we talked about budget and how these projects would be  
18 | supported, I was curious if this is one of the issues that  
19 | came up at your discussion.

20 |           DR. MacGREGOR: No. The funding of specific  
21 | projects really was not discussed. I think there's a  
22 | recognition by all of us in FDA that if this effort is  
23 | successful and we move into further expert groups in  
24 | biomarkers, this is not an insignificant investment just to  
25 | run the necessary meetings and oversee the travel and then

1 | have the necessary scientific dialogue where the expert  
2 | groups are coming back to the appropriate FDA bodies to  
3 | talk about the regulatory science and where it should go  
4 | and data will start coming in, and so on. So, I think  
5 | those are the kinds of issues we discussed, not the  
6 | specific funding of projects.

7 |           But there was a recognition, just kind of in  
8 | passing in the discussion, that yes, the center already is  
9 | focused in this area and certainly would hope to be very  
10 | heavily involved scientifically in projects that would flow  
11 | out of these recommendations.

12 |           MS. WINKLE: I think Jim makes an excellent  
13 | point. We want to be certain that we do have the  
14 | appropriate connection with CDER if this subcommittee were  
15 | to fall under NCTR. I think it's very important from the  
16 | standpoint that obviously those appropriate regulatory  
17 | questions, those questions that are necessary in doing the  
18 | day-to-day regulatory activities of the center -- we need  
19 | answers to those, and it's through this group or through  
20 | the projects that come out of this group that we hope to  
21 | get those answers. So, that connection has to be  
22 | maintained.

23 |           We have looked at several ways and thought  
24 | about several ways they can do this. First of all, I think  
25 | that it's very important that our advisory committee has a

1 member that participates with this group. It has been John  
2 in the past. I think that's a very important liaison back  
3 to the advisory committee. So, I would hope to continue to  
4 do that.

5 Of course, John's term won't last forever. I  
6 think it expires in about a year and a half. I would like  
7 to appoint another person with the toxicology background  
8 that can serve in the same capacity. I think this will be  
9 very helpful in continuing to bring these issues before the  
10 advisory committee and CDER. I think that will help some  
11 of the interaction.

12 I'd also suggest that at periodic times that  
13 maybe the Science Advisory Board out of NCTR could meet  
14 jointly with our advisory committee. We have done this  
15 with other advisory committees in CDER. We find it an  
16 excellent way of really talking about issues and talking  
17 about solving regulatory problems that may relate to two  
18 different advisory groups. So, I would like to propose  
19 that as well.

20 We would continue to have members on the expert  
21 working groups. We already have CDER membership on these  
22 groups. We would hope that they would continue to  
23 participate because again they're part of who understand  
24 the regulate issues that we need to address in CDER's  
25 activities. So, I think that's very important.

1                   And we certainly are open to other suggestions  
2     for keeping this relationship viable. I think it's  
3     necessary that we participate very much in these issues  
4     because again, unless we have projects come to fruition and  
5     the results of those projects are used in the review  
6     process, the decisions that are made by the committee are  
7     really not going to be viable. So, we see the importance  
8     of this and really want to stay part of this activity.

9                   DR. DOULL: Dr. Anderson, Gloria, is also a  
10    member, of course, of the advisory committee.

11                  I had a couple questions. If we had working  
12    groups on imaging and other areas, I guess I'm wondering  
13    are we getting away from tox. That doesn't bother me. In  
14    the sense that NCTR is focused on tox, if you will, and  
15    genomics, there's no problem because they're already big in  
16    that area and hoping to be bigger. But I don't know about  
17    PET scanning and all that, whether that would fit or not.

18                  DR. MacGREGOR: Well, that's a good question.  
19    I'm not sure I know the answer to that. I think in terms  
20    of technical expertise in imaging within FDA, you'll find  
21    that primarily in CDRH, and CDRH is a group that so far  
22    hasn't been too involved here. So, this would be kind of a  
23    future thing maybe to think about in terms of the molecular  
24    biomarker and how you would marry that to imaging, which is  
25    the other follow-on project that the committee had

1 | discussed.

2 |           But the one thing I did want to add to what  
3 | Helen said is I think we already have a very good mechanism  
4 | to ensure the cross-center participation in both the expert  
5 | groups and the subcommittee. That is, at both the  
6 | subcommittee level and at the expert group level, we have  
7 | center liaisons from all the centers that have expressed  
8 | interest in being involved in those activities based on the  
9 | current definition of what they are. So, scientifically I  
10 | think at that level, there's not any need for any change at  
11 | all on the functioning up to the parent committee level.

12 |           The function of the parent committee is going  
13 | to be when this committee and the expert groups kind of  
14 | come to a scientific consensus that they think the body of  
15 | evidence supports a regulatory implementation and a  
16 | recommendation will come out. Then that will go through  
17 | that committee. So, it would make sense to have that be  
18 | the committee that's most knowledgeable in the regulatory  
19 | science that's being addressed.

20 |           In fact, I think the reality is no matter how  
21 | you cut many of these projects, they're going to have to go  
22 | through parts of multiple centers. So, I think in the  
23 | pharmaceutical area, any recommendation or guidance,  
24 | however we set this up, probably ought to go through the  
25 | NCTR for the scientific participation/evaluation, and

1 eventually would have to go through one of the CDER  
2 committees and eventually into the appropriate CDER policy  
3 committee which would then be the arena that would  
4 implement the regulatory.

5 So, it's going to be necessary to maintain  
6 contacts with multiple centers I think. And as Helen  
7 pointed out, I think that ongoing working contact could be  
8 maintained by having representation from the appropriate  
9 CDER bodies on the working groups and on this committee, as  
10 well as on the CDER advisory committee, so there is a  
11 constant report back and feedback from that parent  
12 committee.

13 DR. DOULL: It may be a new ball game. What do  
14 you think about that, Jack?

15 DR. DEAN: Helen did a really nice job of  
16 talking about linkage back to Pharmaceutical Sciences. I  
17 guess my question is how do you propose linkage to the  
18 Scientific Advisory Board at NCTR? Would this be a  
19 subcommittee of the Scientific Advisory Board or would  
20 there be a liaison, or what's the thinking there?

21 DR. MacGREGOR: Well, the specific discussion  
22 is whether to make this a subcommittee of the NCTR Science  
23 Board, rather than a subcommittee of the ACPS. So, that's  
24 the specific thing being discussed. And the reason is all  
25 the reasons that Helen said. The major resources to

1 support this and the scientific interaction and so on, as  
2 the focus is currently defined, has really merged more  
3 closely to the NCTR than to CDER in terms of the scientific  
4 operations, collaborations, et cetera.

5 Now, the concern of the NCTR board was that  
6 eventually recommendations are going to have to come back  
7 into CDER, and you want to be careful you don't distance  
8 yourself from that center. And I think that's an important  
9 thing, that we not distance ourselves from that center.

10 DR. DEAN: Excuse me, Jim, but would there  
11 person from the Scientific Advisory Board on this  
12 subcommittee then? Or would there be someone from here  
13 going and reporting to the Scientific Advisory Board?

14 DR. MacGREGOR: Periodically this subcommittee  
15 reports back to the parent advisory committee, which at the  
16 moment is ACPS, and obtains feedback from that committee  
17 and oversight from that committee. Now, as a routine what  
18 we're considering and what I think the FDA people involved  
19 have come to the conclusion -- we just want to make sure  
20 before we do this -- that, as John said, we don't do  
21 anything that causes a loss of momentum or that causes a  
22 feeling that we've taken an important party and distanced  
23 them from the process. We want to make sure that isn't  
24 happening.

25 But what it would mean simply was that the

1 major reports and feedback would be occurring on a routine  
2 to the NCTR Science Board with one member or two members,  
3 whatever is decided by the CDER committee, also remaining a  
4 member of the subcommittee and reporting back and obtaining  
5 input. But the meetings where we bring all the people  
6 together, where we bring all of you together with all the  
7 Science Board members, that would then be with the NCTR  
8 Science Board rather than the ACPS.

9 DR. REYNOLDS: Well, I guess what I see, if we  
10 need to maintain this, that the NCSS I think has been a  
11 good group to tee up issues that need to have some  
12 scientific exploration through expert working groups. What  
13 I don't see and what I think may be a major charge of this  
14 type of activity, or at least that we're talking about and  
15 perhaps why it's important whether it's affiliated with  
16 NCTR or the Advisory Committee on Pharmaceutical Sciences,  
17 is as I saw this group at least, as we explore the science,  
18 we define diagnostics for biomarkers.

19 What I don't see happening is where drug  
20 sponsors can come and say, well, we think we have a marker  
21 for or we would like to progress this drug in development.  
22 And we already referred to several drugs that are in  
23 development that are on clinical hold, for example, because  
24 of vascular injury, that there's no clear-cut marker or way  
25 forward. What I think this committee, whether it's ACPS or

1 | others -- what I don't see happening very well is the  
2 | ability to come and have this group advise the FDA on how  
3 | one can move forward with these proposals or with these  
4 | protocols. So, to me that's a very important part of the  
5 | process, and so long as that process is maintained or  
6 | available to all drug sponsors or people that develop  
7 | drugs, that to me is the essential process that we need to  
8 | retain.

9 |           And I think certainly in terms of spawning a  
10 | lot of activities that are ongoing now under NCSS, NCTR is  
11 | perfectly capable of doing that. What I want to ensure is  
12 | the linkage back from the data and the science that's been  
13 | generated there to its application to drug development and  
14 | to advising FDA how they would let drug sponsors do  
15 | clinical trials or do assessments to validate, if you will,  
16 | or to further explore the data that you have generated.

17 |           DR. DOULL: Yes. I think in the early history  
18 | of this group, as you know, that's really how it started  
19 | out. We looked broadly for biomarkers in any area that  
20 | would, in fact, be helpful to the clinical development of  
21 | drugs. There were some others besides biomarkers and  
22 | genomics and cardiotoxicity and vascular injury and so on.  
23 | Liver, for example, which ILSI already is in, and there  
24 | were some other areas mentioned. I think that option,  
25 | through this subcommittee, is always a possibility once

1 | things get to the point where they need to be discussed or  
2 | developed or described. That option would always be there  
3 | I would think.

4 | Yes, Joy.

5 | DR. CAVAGNARO: So, then in terms of the  
6 | funding, would it be similar to -- you mentioned NTP. So,  
7 | basically the FDA gets a project through NTP, and at least  
8 | in a previous life when I was involved, each center made a  
9 | proposal and then it would be judged, but the FDA got  
10 | something. It went through and sometimes it varied by  
11 | project or centers gave each other chances to present a  
12 | case that they thought was very important to them.

13 | So, in terms of the NCSS, then we would be  
14 | given discretion to identify things that were important,  
15 | which wouldn't be second-guessed by the NCTR's Science  
16 | Board who's dealing with all the other issues related to  
17 | NCTR. So, when we get to the very important funding  
18 | situation, it would be the recommendation of this  
19 | subcommittee as to prioritization, and we recommend for  
20 | funding. And then that wouldn't get re-prioritized in the  
21 | whole mix of NCTR initiatives that go through their Science  
22 | Board.

23 | DR. MacGREGOR: Well, I think that's not  
24 | correct. I think there are existing mechanisms for  
25 | prioritization of NTP funding and NCTR research funding,

1 and it's not being proposed that this committee would play  
2 a direct role in setting those priorities. What this  
3 committee could do is bring forward a recommendation to  
4 those bodies that we would like to see these funds used in  
5 that way. And then the weight of this committee would  
6 weigh in those decisions.

7 So, for example, there is a committee for NTP  
8 funds' use that includes representatives from all the  
9 center as well as NTP from outside FDA.

10 DR. CAVAGNARO: Oh, no, no.

11 DR. MacGREGOR: And they set those priorities,  
12 but the recommendations come through FDA.

13 DR. CAVAGNARO: Yes, right. That was an  
14 analogy. Right.

15 So, would it be similar to the way that is  
16 funded? That was the question. Would the NCTR look at  
17 this as a recommendation by NCSS that's been vetted through  
18 this subcommittee? And that's the recommendation, so that  
19 would be the recommendation.

20 DR. MacGREGOR: Well, as far as NCTR funding  
21 and research programs, this subcommittee would then become  
22 a part of that process; that is, it would be a part of that  
23 advisory committee that does advise NCTR on the use of its  
24 funds. There are two different processes: one for funds  
25 that are part of NCTR's FDA-funded and one that's part of

1 NTP.

2 DR. CAVAGNARO: Right.

3 DR. MacGREGOR: And they're two separate  
4 processes for prioritizing.

5 DR. CAVAGNARO: I was talking about the NCTR  
6 because that's what this committee would be under.

7 DR. MacGREGOR: Right. It would become then a  
8 part of the advisory committee that advises on that, yes.

9 DR. DOULL: Frank.

10 DR. SISTARE: We look to NCTR for funding. So,  
11 would this compete with other initiatives at NCTR, other  
12 research initiatives that NCTR is involved in? We're not  
13 looking for extra money anywhere. We're looking to compete  
14 with their existing budget?

15 DR. MacGREGOR: I'm not sure I would put it  
16 that way. Let me rephrase your question I guess. Let me  
17 restate it in the way that I just said.

18 At the moment, there is a Science Advisory  
19 Board at NCTR that advises the NCTR on the quality of its  
20 programs, the focus it's taking, and how it should be  
21 spending its FDA appropriated research funding. If the  
22 subcommittee moves to that advisory committee, it becomes a  
23 part of that advisory committee and will then make  
24 recommendations to the NCTR management about the management  
25 of those research funds and how they're being used and how

1 they should be used. We're not proposing moving any block  
2 of money anywhere because there is no block of money to  
3 support research from this group at the moment.

4 DR. DEAN: I'm not sure what the issue there  
5 would be because we actually go from a zero budget to at  
6 least having a budget that we can request funds from.  
7 Maybe I'm a little naive, Frank.

8 DR. SISTARE: Well, let's review the history of  
9 how these initiatives got to where they are. I was a  
10 little confused by Jim's comment that there was already  
11 some collaborative mechanisms in place at NCTR to do these  
12 things.

13 These efforts were brought to the forefront  
14 because of close discussions between researchers in CDER  
15 and reviewers in CDER. What are some of the vexing  
16 toxicities. What are some of the safety issues that are  
17 haunting, that keep coming up, keep recurring, and are not  
18 being solved? And I presented something here a while ago,  
19 and I listed a panoply of these, four, five, or six or  
20 seven of these things. Some of the more mature that the  
21 research lab in CDER had some ongoing momentum had some  
22 sort of like R01 data, preliminary data kind of thing, that  
23 gave maturity to the project, were the ones that surfaced.

24 So, that process worked very well because there  
25 was very close interdigitation between researchers who felt

1 | there's a way to do things better and reviewers who have a  
2 | charge. They've got to review petitions on their table.  
3 | They have to make decisions here and now, and they're going  
4 | to do it the best way they can. But they're not thinking  
5 | about 5 years from now, 10 years from now, what's a better  
6 | way of doing things, but the researchers, working closely  
7 | with them, sitting in the same committees with them, are.

8 |           The one danger that we have to be careful about  
9 | with NCTR is just a geographic one and the lack of  
10 | interdigitation in ongoing committees, the lack of ongoing  
11 | communication in terms of the fine tuning. We have two  
12 | projects very well scoped out now. There's momentum there.  
13 | There's momentum there because there's ongoing laboratory  
14 | research there. There are collaborators that have been  
15 | brought to the table through things like CRADAs, funding  
16 | mechanisms, from sponsors who also share the same issues,  
17 | the same concerns. So, the sponsors are willing to put  
18 | money on the table to get these problems solved.

19 |           What's going to happen five years from now when  
20 | there are other issues? How are those problems going to be  
21 | surfaced? How is this process going to continue? How is  
22 | it going to perpetuate, to continue to evolve, to continue  
23 | to ensure that we evolve to ensure that the best questions  
24 | are being asked and the most important problems are being  
25 | addressed? That's something I think we have to be careful

1 about if we split off into NCTR. We don't have a CDER  
2 member on the NCSS right now.

3 DR. DOULL: Let me back up and ask. Our  
4 working groups have come specifically to NCSS saying we are  
5 planning something that will require funds. We are  
6 thinking about places that we could go to ask for that  
7 money. The issue then is, does that come through this  
8 subcommittee? Do they come to this subcommittee and say,  
9 help us go to NCTR or to ILSI or whoever to get money? Or  
10 are they on their own out there to go to those places and  
11 get money?

12 I think what the subcommittee wants to do is to  
13 help them get the money to do these jobs, and the question  
14 is, are we involved in all this money-raising thing? Do we  
15 go to ILSI with you guys to help you get the money, or do  
16 we say you're on your own to get the money? I guess I'm  
17 not clear exactly how best we can help our working groups.

18 DR. MacGREGOR: My understanding is that the  
19 subcommittee or any FDA committee cannot play a role in  
20 fund-raising and FDA can't fund raise. But what you can do  
21 is you can help us identify where is the science that can  
22 improve our regulatory practice and where's the common  
23 interest between people that develop products and people  
24 that regulate products to do that more efficiently and  
25 produce better products, and where are there existing

1 resources that, if they could be brought together by  
2 appropriate mechanisms, could bring that to fruition.  
3 That's the role of the committee, not fund raising. There  
4 are mechanisms to bring the funds to bear to do things if  
5 the opportunities and the directions are identified, and if  
6 all the parties agree they want to go there, then there are  
7 other mechanisms that can make that happen and become  
8 funded.

9 DR. DOULL: Okay. So, what you're saying is  
10 our role is to encourage that and to support it by writing  
11 letters and what have you, but it is the working groups  
12 that will actually do the asking for money, so to speak,  
13 not us.

14 DR. MacGREGOR: No. Working groups won't ask  
15 for money either, I don't think. Working groups will  
16 identify what it would be useful to do, ways of doing them,  
17 how groups could be brought together, and then groups that  
18 have appropriate relationships to fund, which are doing  
19 that at the moment, can do that. And we've talked about  
20 some examples. So, ILSI consortia is one example. NTP  
21 funds is another example, and there's a list of examples  
22 that have already been identified as possible ways to fund  
23 these things.

24 The important thing, I think, for this group to  
25 do is to set the direction that we should be taking and

1 pull the collaborators together, the internal and external  
2 stakeholders to the whole process of pharmaceutical  
3 development to develop a consensus on what's important to  
4 do that actually could be done.

5 DR. DOULL: Jack, you're on HESI over there.  
6 You know how that works. People come in and say, hey, I  
7 need some money to do this. Or I'm on RSI. That's what  
8 happens to us. People come and say, hey, we need this, we  
9 need some money to do this thing, and you say, yes, it's a  
10 good idea and say to ILSI or whoever, why don't we fund  
11 this thing? I'm not exactly sure how we can help with the  
12 mechanics of it. I hear what you're saying, Jim, and we  
13 need to figure that out.

14 Gloria, help us out.

15 DR. ANDERSON: I don't have an answer to the  
16 money question.

17 I think there are several issues here on the  
18 table, and let me say right up front I don't have any  
19 problem with the transfer of the responsibility, I guess it  
20 is, to your agency.

21 But I'd like to go back to the original goals  
22 of this committee which I thought you did an excellent job  
23 of defining.

24 First of all, I'm having difficulty making the  
25 leap from the goals and objectives in your original

1 background paper, which we're reminded of each time we get  
2 a document, which makes it easier to prepare for the  
3 meeting, but I'm having difficulty making the leap from  
4 those goals to where we are now in terms of what the expert  
5 working groups are doing. But perhaps that's my problem.

6 The thing that I would like to point out,  
7 however, is that it was my understanding based on the  
8 problems that you defined, problems you defined initially,  
9 which this subcommittee was to address, that the expert  
10 working groups which were created were addressing only a  
11 small portion of what was a larger problem in the drug  
12 development industry. Am I correct in that?

13 DR. MacGREGOR: Yes.

14 DR. ANDERSON: Now, if that is in fact the  
15 case, if the responsibility for what is happening now is  
16 handed to an agency that does toxicology research, what  
17 happens with the ongoing discussions or the potential for  
18 ongoing discussions about other problems that are related  
19 to bridging the gap between the nonclinical studies and  
20 clinical studies and increasing the predictive value of  
21 nonclinical studies?

22 And I hope I said up front I'm not against what  
23 you're talking about. That's just a lingering question in  
24 my mind.

25 DR. MacGREGOR: I think Frank made an excellent

1 point. Where did the issues that we identified come from?  
2 The principal place they came from were twofold, I think,  
3 discussions that happened among essentially the  
4 subcommittee and people that are in the room, number one.  
5 And number two is we went to the CDER Pharm Tox Research  
6 Coordinating Committee, of which Frank is co-chair, and we  
7 said, how do the CDER regulatory scientists see this? What  
8 do you see as the major problems in your view? And that's  
9 really where the specific two problems of the cardiotox and  
10 the vascular injury arose from, were recommendations from  
11 that committee based on current activities, largely by  
12 Frank's lab driven by really the regulatory issues and  
13 recognizing the potential to make much greater progress if  
14 various external parties might be drawn in in an effective  
15 way to solve those two problems.

16 So, that's really the way it happened, and I  
17 think the way it would continue to happen. That part  
18 wouldn't change at all. That is, we'd go out to the  
19 centers and we'd solicit their input from those kinds of  
20 committee into this group, which was constituted to be a  
21 knowledgeable group to evaluate that kind of information  
22 and make recommendations. So, all that would be  
23 essentially the same as it has been.

24 DR. ANDERSON: I guess my question, if indeed  
25 it were a question, was not clear. My understanding is

1 that the currently existing expert working groups have a  
2 specific responsibility in a specific area. Perhaps I  
3 should rephrase the question then.

4 If these two groups solved the problems that  
5 they are addressing now, will that solve the problem that  
6 you identified in the original document and will it address  
7 all the goals that are listed there? Because if that does  
8 not happen, it means then that there is a need for someone  
9 to address whatever is left, and even if the responsibility  
10 for what is now taking place is sent to another group --  
11 and I'm agreeing with that -- then who will address or how  
12 will the other parts of the problem be addressed?

13 DR. MacGREGOR: Well, in my view the background  
14 paper that you're referring to basically makes the argument  
15 or identifies a number of areas of scientific advance that  
16 those of us involved in putting it together felt presented  
17 opportunities to improve both drug development and drug  
18 regulation and identified some of those scientific bases of  
19 how they might be brought to fruition. Really that was the  
20 reason that this subcommittee was created. It is this  
21 subcommittee's charge to evaluate those opportunities and  
22 to make recommendations on how to bring stakeholders  
23 together to pursue those opportunities. That's really the  
24 charge of this subcommittee.

25 In other words, I think what you're asking is

1 | how would that change if the subcommittee is moved to a  
2 | different oversight committee. In my mind, that part  
3 | doesn't change at all. That is, this subcommittee was  
4 | constituted of experts that ought to be able to address  
5 | those issues and make those recommendations.

6 |           Shall I say this in public? I don't know, but  
7 | I will I guess. My belief is that probably there could  
8 | have been a specific advisory committee just charged for  
9 | this if it weren't for kind of technical reasons that exist  
10 | within FDA that necessitated this effort to be part of an  
11 | existing advisory committee. So, in a sense this committee  
12 | has been constituted in a way that it holds public meetings  
13 | and it sets a direction and it is charged to do some things  
14 | that advisory committees really haven't done before, which  
15 | is to not just identify areas and provide advice, but try  
16 | to actually facilitate the implementation of that advice.  
17 | So, that's the thing we're on the verge of addressing now  
18 | that we're hoping that this subcommittee will be able to  
19 | do.

20 |           DR. ANDERSON: This is the last thing I'll ask.  
21 | What I've heard this morning is we're transferring  
22 | responsibility for the current expert working groups, that  
23 | piece of it, or are we transferring responsibility for the  
24 | Nonclinical Studies Subcommittee to another area? That's  
25 | the question I'm raising because I think it's important.

1 The answer may be important to achieving the goals that are  
2 set forth in the original document.

3 DR. MacGREGOR: If I understood you correctly,  
4 the responsibility for the expert groups resides with this  
5 subcommittee, and that part won't change. But this  
6 subcommittee recommends to the parent committee when it's  
7 time to make a scientific recommendation to the parent.  
8 That's what would change.

9 So, the question really is this committee is  
10 charged with the responsibility for implementing this  
11 backgrounder, and the question is, what's the best parent  
12 committee to dialogue with and to present recommendations  
13 through and what's the best mechanism for kind of  
14 overseeing and facilitating that? I think that's the  
15 question.

16 DR. DOULL: Yes. When the subcommittee was set  
17 up, the two groups that we have expert working groups on  
18 are the two groups that are most mature and ready for that.  
19 Imaging we looked at and thought maybe, but it wasn't quite  
20 ready. Genomics, we're not exactly sure. So, down the  
21 road potentially there's a whole batch of additional  
22 working groups that might be formed as these sciences come  
23 up to the point where they need expert working groups to be  
24 brought about.

25 The other issue then is once these committees

1 develop a good methodology, solve the problem, as you say,  
2 Gloria, then the question is how does one bring that  
3 information into a recommendation and back into the agency  
4 where it can, in fact, improve clinical use. That I think  
5 is the issue, as Helen has pointed out and Jim has pointed  
6 out, that is of some concern. This subcommittee needs to  
7 have the ability to do that, to bring that information to  
8 the agency in a way that will help improve drug development  
9 and use.

10 DR. MacGREGOR: I notice Joe DeGeorge has  
11 arrived. Part of this discussion that we're having at the  
12 moment is to be sure that we're maintaining the connection  
13 between the regulatory implementation and also  
14 identification of the regulatory science needs. Joe, as  
15 I'm sure everybody knows, is chair of the CDER Pharm Tox  
16 Coordinating Committee, which is the regulatory body to  
17 which these kind of recommendations ultimately would go and  
18 it is also the parent of the Research Subcommittee that  
19 provided this group with the initial recommendations on  
20 these two areas of cardiotox and vascular damage that we're  
21 pursuing. So, Joe, do you want to comment on your views?

22 DR. DeGEORGE: Thank you.

23 I was listening to the discussion and I think  
24 it's interesting. Frank raised the point I think people  
25 are concerned about, and that is, is the connection going

1 to be maintained to the regulatory center and, in  
2 particular, to CDER? I think that there is a possibility  
3 that the committee may have valuable information and gain  
4 valuable insights from other centers such as Biologics and  
5 their aspects that might be more centralized if, in fact,  
6 were part of the reporting to the NCTR committee because  
7 they can address biologics issues, not just CDER's concerns  
8 about cardiovascular toxicity or more vascular toxicity.

9 I think our center would continue to function  
10 with its researchers and with its evaluators, regulatory  
11 review staff, to identify issues that are of concern. We  
12 identified two that were thought to be mature enough to  
13 take on, and I think we'll identify some other ones as they  
14 come along as well and they'll surface through our  
15 committee and we'll make recommendations that we think need  
16 to be pursued in terms of developing approaches to address  
17 these problems. And I don't see why they would not flow  
18 back through a committee, which in fact is now situated in  
19 the part of the FDA whose mandate is to address these  
20 problems.

21 The mandate of NCTR is, in fact, to develop  
22 methodology to support regulatory decisions in relation to  
23 toxicology, and I might expand that to safety not just  
24 toxicity, if we're thinking only of the nonclinical  
25 aspects. Clearly a lot of the work they're doing down

1 | there has to do with biomarkers that are looking in humans,  
2 | not necessarily looking in animals for outcomes.

3 |           So, I don't see that there's any difference in  
4 | the process, with the exception that the committee will be  
5 | at that point part of a committee that influences -- not  
6 | directs, but influences -- the conduct and direction of  
7 | research for a substantial portion of FDA's budget -- that  
8 | is, the budget of NCTR -- and could respond to the various  
9 | centers, not just CDER, but other centers. But clearly  
10 | we'll keep our voice loud enough to be heard even if it is  
11 | in Arkansas. So, I don't think there's any problem with  
12 | that. So, I hope I can help.

13 |           DR. DOULL: Frank?

14 |           DR. SISTARE: I think the mission of the NCTR  
15 | is more focused. Jim, do you know the exact verbiage for  
16 | the mission? I think it's fundamental toxicology research.  
17 | That's really their charge. They do support the other  
18 | centers, but I believe their mission is focused on  
19 | fundamental toxicology mechanisms, applications, these  
20 | kinds of things. The mission of the Center for Drugs is to  
21 | ensure that safe and effective drugs are available to the  
22 | American public. A subtle, but very important  
23 | philosophical difference there. The Center for Drugs is  
24 | focused on making sure that drugs are safe. NCTR asks and  
25 | answers very important questions regarding risk assessment

1 with respect to toxicity questions and what might the  
2 relevance be to people. Subtle but it's distinct.

3 The other thing is the Center for Drugs is very  
4 closely intertwined with the drug development process.  
5 NCTR is not. They're very talented researchers focused on  
6 toxicology issues. These questions are problems because  
7 they are involved in stymieing progress in the  
8 developmental pipeline.

9 Ensuring a dialogue with a research view that's  
10 focused on very critical safety issues that are hindering  
11 that process is something that has to be ensured. I don't  
12 know what the best mechanism is. I don't know what the  
13 best mechanism is. I'm expressing some concern. That's  
14 all, by transferring it to a center with a different  
15 mission.

16 DR. REYNOLDS: I think one of the things that's  
17 important is to see the role of this Nonclinical Studies  
18 Subcommittee. To me, it's kind of an oversight body, a  
19 steering committee, for doing this basic research, and I do  
20 like the notion of safety, not just toxicology per se. So,  
21 I think that NCTR can do that well, in fact maybe better  
22 than what's going on now, not to be judgmental.

23 But I do echo what Frank and Joe and others  
24 have raised, that the mechanism for getting out what are  
25 the issues for CDER, that is, in the reviewing divisions,

1 | what are those issues that impede drug development and  
2 | impede our ability to make decisions about safety.  
3 | Identifying those issues I think we have done very well.  
4 | And I think Frank said it pretty clearly, that what we need  
5 | to make sure of, wherever the oversight lies, is that that  
6 | information comes back to the reviewing division that  
7 | individual reviewers and decision makers within those  
8 | divisions can take advantage of what has the Vascular  
9 | Injury Working Group decided, what is an appropriate  
10 | measure of vascular injury in a clinical trial, phase I,  
11 | phase II, or phase III, so we can progress drug  
12 | development.

13 |               So, where this reports to to me is not so much  
14 | an issue as it is we need to ensure that the processes in  
15 | place for getting the ideas to the researchers and then  
16 | getting the outcome, the experiments, and the results of  
17 | the experiments back to the people that need to use them.  
18 | If we ensure that, which I am sure we can, then I'm  
19 | comfortable wherever this might be.

20 |               DR. DeGEORGE: I'll just make a comment, Jack.  
21 | First of all, it's not like this is a new process to us in  
22 | terms of developing new approaches. Transgenic animals  
23 | were not done within CDER. They were done by a  
24 | collaboration. In fact, they were done at the NIEHS's  
25 | facility. We looked at that information. We made

1 | determinations that we could use that information in  
2 | regulatory decisions. So, clearly if the science is  
3 | brought and a case is strongly made for it, we can find a  
4 | way to incorporate that into the regulatory process.

5 |           The working groups are supposed to identify how  
6 | to solve the problem, what is the state of the problem,  
7 | what is the state of the science, and what needs to be done  
8 | to solve that. And then someone has to do it. It may be  
9 | that NCTR is not interested to do that, but perhaps this  
10 | committee, working through their parent committee, would  
11 | make recommendations that some other group does it, NTP  
12 | does it, NIH does it, FDA CDER does some of it, and that  
13 | they try to make a recommendation this is important  
14 | research, it should be done. And then when the outcome is  
15 | available, we'll find ways to incorporate it into our  
16 | regulatory process. Whether it's done under a parent  
17 | committee that's part of CDER or a parent committee that's  
18 | part of NCTR, that won't really influence us because the  
19 | other processes were done and made recommendations that  
20 | didn't come out of any parent committee related to the FDA  
21 | at all. So, clearly we'll use the information.

22 |           So, the feedback loop that you seem to be  
23 | concerned about I don't think is going to be any different  
24 | in the future than it is now. You might actually have an  
25 | opportunity to get to influence the support because you're

1 | working through a committee that actually has the resources  
2 | to garner some support.

3 | DR. DOULL: Joy?

4 | DR. CAVAGNARO: I was the ex officio member to  
5 | the committee for CBER, the NCTR committee. So, it's like  
6 | deja vu. There was always opportunity for centers to  
7 | interact. As you know, that was a big thing -- I don't  
8 | know -- five-seven years ago, this interaction with the  
9 | various centers and NCTR.

10 | I guess I see the difference here -- again, to  
11 | go through the prioritization -- is if we've identified  
12 | issues that are the critical issues to address, is no an  
13 | acceptable answer for research? I mean, right now we're  
14 | coming down to the point of funding. All of this, wherever  
15 | we end up in terms of oversight, the bottom line is still  
16 | going to be funding these initiatives that for the past two  
17 | years we've identified as the key initiatives. Whether or  
18 | not we all agree that they're the key initiatives, they  
19 | ended up being the key initiatives, if nothing else, to  
20 | serve as a prototype of an interaction between academia and  
21 | industry and government, to answer the question.

22 | So, I guess my question is, when we ever get to  
23 | the discussions in terms of funding, which clearly has to  
24 | happen for the vasculitis to meet any goals and cardiotox  
25 | might be a little bit better served because there's more

1 data, but there still needs to be resources to address some  
2 of those issues, will somebody still go forward? Will  
3 Frank's group still go forward trying do something? Will  
4 drugs still be on a clinical hold until we go forward?  
5 That's the piece that I am totally not understanding.

6 MS. WINKLE: Joy, I think you bring up some  
7 really good points. I don't think we're going to solve the  
8 oversight of this group sitting here at this table. I  
9 think that there have been a lot of issues that have been  
10 brought up today that are very, very important. I think  
11 the things that we need at FDA to do, when we go back to  
12 the table, is make certain that the interactions do remain  
13 here, that many of the questions that have been surfaced  
14 today, as far as continuing with these projects, how future  
15 projects will be done, how CDER will stay involved, need to  
16 be put on the table and we need to discuss them further.  
17 There have been issues brought up here today that I have  
18 really, truly not thought of. So, I think this discussion  
19 has been extremely valuable as we go forward.

20 I think what we're talking about here, though,  
21 mainly is oversight of this committee, and I think the  
22 important thing is that the projects we've already  
23 identified continue to move forward, whether the oversight  
24 is at NCTR or if it's at CDER. These are very important  
25 projects. I think the whole success of this subcommittee,

1 | regardless again of the oversight, is going to be based on  
2 | these projects moving forward.

3 |           I have been very involved with the Product  
4 | Quality Research Institute, which I think some of you all  
5 | know about. We've had a very, very difficult time moving  
6 | forward with our projects. You all are actually farther,  
7 | in some ways, with the two projects you have in identifying  
8 | what needs to be done than we've been able to get to at  
9 | PQRI. And still, it's important to think through all of  
10 | the issues and all of the process and stuff, but that's not  
11 | the important thing. That's not where the focus needs to  
12 | be. The focus needs to be on these two projects, getting  
13 | them done, moving ahead.

14 |           And I think a lot of the questions and issues  
15 | that have come out here today will sort of sort out as you  
16 | do some of this stuff. As you look for dollars, as you  
17 | identify how the dollars are going to get, I think that  
18 | automatically you're going to see the interactions that  
19 | need to take place, whether it's with the industry or  
20 | whether it's internally within FDA.

21 |           So, again, we need to go back. Jim and I, Dr.  
22 | Casciano need to talk more about the process, the issues,  
23 | and make sure that they're in line so that we can ensure  
24 | the success of the subcommittee regardless of oversight.  
25 | Again, I really think it's necessary for you all to focus

1 on the projects and getting them done.

2 So, unless Jim has any other thoughts on where  
3 we need to go from here. Again, I think a lot of things  
4 have come up that have been very important. So, I  
5 appreciate the conversation.

6 DR. DOULL: I think that's a very good point,  
7 Helen. We can't solve all these immediately, but at least  
8 we now know what we have to get to and how to do it.

9 One thing about getting involved with NCTR, I  
10 was involved with Bern Schwetz a lot when he was the  
11 director down there. Part of the thing is just talking to  
12 those people. They need to hear what the concerns of this  
13 subcommittee are, and I think that is an important issue,  
14 is to take that message to them. We need to figure out  
15 ways in which to do that.

16 Jack?

17 DR. REYNOLDS: Just a quick comment.

18 DR. DOULL: We need to have the public  
19 discussion.

20 DR. REYNOLDS: Just one quick comment. I think  
21 that we can't solve the problems here of where this  
22 reports, but I think what we can do is raise concerns that  
23 we have. I've not heard any major concerns here raised by  
24 any of the committee members on where this is reporting to,  
25 but I think it does have to be an administrative decision

1 | for you all. So, I think that was to me the outcome of the  
2 | dialogue. We have concerns, I guess, collectively as a  
3 | group where this group lies administratively.

4 | DR. DOULL: So, I will assure the chairs of the  
5 | working groups that we're in your corner and we're going to  
6 | figure this out and help you in some way as best we can.

7 | We need to ask if there is any public  
8 | discussion. Have we had any requests?

9 | MS. TOPPER: We've had no requests.

10 | DR. DOULL: So, we just need anybody who has a  
11 | burning concern a chance to air it. I don't see any  
12 | burning concerns.

13 | Are there any other issues that we need to do,  
14 | Helen, for this group?

15 | DR. HOLT: Just a very brief point. But being  
16 | from a corporate background myself, I think of these  
17 | things. Wherever this committee sits and whatever we do,  
18 | particularly on the vasculitis program, I've understood, if  
19 | it is going to succeed, there will be new things that will  
20 | be found and whatever is done, whatever mechanism is taken,  
21 | I urge everybody to be cautious that what could happen --  
22 | it's happened before -- is that through the great skill of  
23 | publicly funded things, that if it's exclusively publicly  
24 | funded, it actually ends up making important information  
25 | that is by definition not a good product.

1                   And that's one of the things on a biomarker,  
2                   what makes for an ideal biomarker. The very last thing on  
3                   there is that it's commercially viable. And there are  
4                   certain things that you guys you can do inadvertently that  
5                   will make it so that it's not commercially viable like a  
6                   full disclosure of information before there can be  
7                   intellectual property taken and so on. So, in the  
8                   background, just one of the things that I would encourage  
9                   is if there's funding mechanisms or whatever, that there be  
10                  some sensitivity to make sure that whatever is done in  
11                  finding new and important things, that it doesn't sort of  
12                  get in the way of eventual commercialization, which frankly  
13                  is not part of FDA at all, at least my understanding.

14                  DR. DOULL: Yes. That's a legitimate concern.  
15                  I think the subcommittee needs to keep that in mind.

16                  Any other final points? Jim, do you have  
17                  anything more?

18                  DR. MacGREGOR: No.

19                  DR. DOULL: The parent committee is meeting the  
20                  end of this month, but we are not scheduled to report to  
21                  the parent committee at that meeting, as I understand. The  
22                  agenda came out the other day, Helen. There was nothing on  
23                  there.

24                  MS. WINKLE: We will have some time set aside  
25                  just for reports back from the subcommittees. I think as

1 | you all know, the advisory committee actually has three  
2 | subcommittees. It's getting ready to take on two more.  
3 | So, it's a very active committee. We're taking on a  
4 | subcommittee on emerging technologies and manufacturing,  
5 | and we're also taking on the subcommittee for risk  
6 | management for the center. We're going to set up a  
7 | subcommittee within our advisory committee. So, this is  
8 | going to be a very active advisory committee. So, we will  
9 | have a time set aside at each meeting where we report back  
10 | from the subcommittees.

11 |                 DR. DOULL: Well, on your behalf, Gloria and I  
12 | will give them a quick report on the progress at this  
13 | meeting.

14 |                 MS. WINKLE: I appreciate it. I think it would  
15 | be very helpful to update them just briefly on where the  
16 | two working groups are and to get their buy-in for  
17 | continuation of the efforts that are being put forth.

18 |                 DR. DOULL: No other comment?

19 |                 (No response.)

20 |                 DR. DOULL: Thank you. We are adjourned.

21 |                 (Whereupon, at 11:42 a.m., the subcommittee was  
22 | adjourned.)

23 |  
24 |  
25 |

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