

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

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FOOD AND DRUG ADMINISTRATION

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CENTER FOR BIOLOGICS EVALUATION AND REVIEW

BIOLOGICAL RESPONSE MODIFIERS ADVISORY COMMITTEE

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THURSDAY

JANUARY 30, 1997

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OPEN SESSION

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The Advisory Committee met in Conference Room 4108 at 11400 Rockville Pike, Rockville, Maryland, at 3:00 p.m., Julie M. Vose, Chair, presiding.

PRESENT:

JULIE M. VOSE      Chair  
HUGH AUCHINCLOSS      Member  
ELLIN BERMAN      Member  
MALCOLM BRENNER      Member  
PAMELA HARTIGAN      Member  
RICHARD HONG      Member  
EUGENIE KLEINERMAN      Member  
ABBEY S. MEYERS      Member  
CAROLE MILLER      Member  
ROBERT T. WOODLAND      Member

ALSO PRESENT:

DAVID S. FINBLOOM      CBER  
WILLIAM FREAS      CBER  
NEIL GOLDMAN      CBER  
JAY P. SIEGEL      CBER

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

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Overview of the Division of Cytokine Biology and the Laboratory of Cellular Biology, David S. Finbloom . . . . .	10

1 P-R-O-C-E-E-D-I-N-G-S

2 (3:20 p.m.)

3 DR. FREAS: Dr. Vose, can you hear us? Dr. Vose, are  
you able to hear us?

5 CHAIRPERSON VOSE: I'm here.

6 DR. FREAS: If I could have everybody's attention, I  
think I will go through and try to make sure that everybody is on  
line and we'll get the meeting started.

9 First of all, Dr. Vose, could you just say hello to us?

10 CHAIRPERSON VOSE: I am here. How is everybody there?

11 DR. FREAS: Okay. Next, Dr. Hong, could you say hello  
to us?

13 DR. HONG: Hello from cold Burlington.

14 DR. FREAS: Okay. Now I have not seen Dr. Carole  
Miller. Dr. Miller, are you on board?

16 Okay. We have not been able to connect with Dr. Miller  
yet

18 Dr. Auchincloss, I have seen you. Can you hear us loud  
and clear?

20 DR. AUCHINCLOSS: I can hear you loud and clear.

21 DR. FREAS: Good. Dr. Hartigan, are you still with us?  
Dr. Tamala Hartigan in Connecticut?

23 Okay. She was with us earlier. I am sure she will  
join us momentarily.

25 Dr. Woodland, yes, you are there. You can still hear

us loud and clear?

2 DR. WOODLAND: Yes. I do.

3 DR. FREAS: Okay. To our friends in the video  
4 conferencing.

5 DR. WOODLAND: Can you hear me?

6 DR. FREAS: Yes. We can hear you loud and clear. We  
7 are having no problem with the video conference at this time. We  
8 did drop everything and we appreciate you bearing with us.

9 To the people on the video conference, would you please  
10 write down this number. Should we drop you again on the video  
11 conference, we would want you to telephone in and be part of the  
12 teleconference because we would like to get this meeting over  
13 tonight.

14 If you need to call us and be part of the  
15 teleconference, please dial 1-700-288-2000. You would ask for  
16 teleconference number R24001. I will repeat that number again.  
17 That's 1-700-288-2000, teleconference number R24001.

18 Now for the people who are on the videoconference, let  
19 me introduce to you the people who are on the teleconference.

20 Abbey Meyers, are you still on the teleconference line?

21 MS. MEYERS: Yes. I'm here.

22 DR. FREAS: Could you speak up just a little bit? I  
23 want to turn this up and ask Dr. Vost if she can hear us.

24 Dr. Vost, can you hear Abbey Meyers?

25 MS. MEYERS: Can you hear me?

1 DR. FREAS: I can hear you. I am going to try to see  
if Dr. Vost can hear you. The volume on this is as loud as it's  
going to get. Can we relocate this --

4 CHAIRPERSON VOSE: Have her speak up again. I can't  
hear her.

6 DR. FREAS: Abbey, could you speak as loud as you can?

7 MS. MEYERS: Yes. Good morning. How are you? This is  
Abbey Meyers.

9 DR. FREAS: Dr. Vost --

10 CHAIRPERSON VOSE: I can't hear anything.

11 DR. FREAS: Okay. Let me just go to Dr. Kleinerman.

12 DR. KLEINERMAN: Present and accounted for. We must  
finish by 6:30 because I have a golf lesson.

14 DR. FREAS: Dr. Vose, are you able to hear Dr.  
Kleinerman?

16 I have been asked to ask everybody to turn your mute on  
if you are not talking, but please be sure to turn your mute  
button off when you get ready to talk.

19 We are still experiencing a few difficulties, Dr.  
Brenner. Let me just check.

21 Dr. Vose, can you hear us?

22 CHAIRPERSON VOSE: I can hear you fine.

23 DR. FREAS: Can you hear Dr. Brenner or Dr. Kleinerman  
on the telephone?

25 DR. BRENNER: Yes. I can hear you fine. You are

looking a bit blurry around the edges though.

2 DR. FREAS: Let me just -- Dr. Vose --

3 CHAIRPERSON VOSE: I can hear them fine.

4 DR. FREAS: Okay. If for some reason anybody has  
problems with the video portion, we can always hook you in on  
that conference call by that 1-700-288-2000 number. I would like  
to give everybody a few seconds to -- you know, I know if you  
can't hear me, you aren't going to respond, but if there's a  
problem, please just dial into that 1-700-288-2000 number,  
conference 24001, and participate by telephone instead of video  
if there's a problem and you can not hear us.

12 Dr. Vose, at this time, I would like to try to proceed  
with the meeting. I am assuming that if somebody can't hear us  
or communicate with us, that they will telephone on that  
telephone number.

16 This is the first time, as you all know, that we have  
attempted this. We appreciate you bearing with us on this  
attempt to video us all in.

19 Let me go ahead and introduce to the people who do not  
see who have a cloudy video, and tell us exactly what is  
happening in this room. In this room right now we have Dr.  
Finbloom, who is Director of Cytokine Biology, Acting Lab Chief  
of the Lab of Cell Biology. He will be presenting an overview to  
us about two minutes.

25 Sitting next to Dr. -- Dr. Woodland, can you hear us?

1 DR. WOODLAND: Yes. I can. Can you hear me?

2 DR. FREAS: We hear you. Everything appears to be  
fine3 I am just trying to tell the people who are on the  
tele4 phone --

5 DR. WOODLAND: I noticed you thought it was me that  
cause6 d the interference.

7 DR. FREAS: You are the only one I see on the screen,  
Dr. W8 oodland. I didn't mean to pick on you. You are the only  
one 9 I knew who was there.

10 Getting back to the people on the telephone. In this  
room11 in addition to Dr. Finbloom, we also have Dr. Jay Siegel,  
Dir12 ector of OTRR, you are sure aware of him. We also have Dr.  
Neil13 Goldman, who is Associate Director for Research for the  
Cent14 er of Biologics. We have Dr. Gene Murano, Director of  
Sci15 ence for the Office of Therapeutics.

16 Behind me are the people who are involved in the site  
visi17 t. They are -- I know you can't see them on the telephone,  
but18 they are Dr. Kurt Stromburg -- can you focus a camera on Dr.  
Kur19 tStromburg? We'll go around the room.

20 Okay. Joyce Pegues, next to Dr. Stromburg. Gibbes  
Joh21 n. Next, Barbara Wilcox, and Donald Fink. That's  
eve22 rbody in the room with the exception of our transcriber. We  
have23 a new member to the Advisory Committee team who is Rosanna  
Har24 vy. She is taking Pearlina Muckelvene's place, because  
Pea25 rline is on her way down to Norfolk, Virginia.

1        So I would like to welcome everybody. Dr. Pamela  
Hartigan, I see you are back on. If you get lost again or get  
dropped, would you please write this number down. The  
teleconference number is 1-700-288-2000, ask for conference  
number 24001, and we'll have you on the telephone as opposed to  
on video if there's serious video problems.

7        DR. HARTIGAN: Say that again, Bill?

8        DR. FREAS: It is 1-700-288-2000, conference R24001.

9        Okay. Again, I have been asked, this conference will  
progress much more satisfactorily if everybody would push the  
mute button when you are not talking. You have got to remember  
to flip the mute button off when you are talking, but please push  
the mute button to keep down the static.

14       Okay. Dr. Vose, I would like to proceed with the  
meeting with your permission.

16       CHAIRPERSON VOSE: Please. Go ahead.

17       DR. FREAS: Okay. At this time, Dr. Vose, we have to  
have an open public hearing. I don't think there's anybody  
around who would be brave enough to try to venture to address the  
committee at this time, and I don't see any volunteers in the  
audience. So with your permission, I would like to call an end  
to the open public hearing and then introduce Dr. Finbloom to get  
on with his site visit overview.

24       CHAIRPERSON VOSE: Please, proceed with that.

25       DR. FINBLOOM: Okay. I am going to give a very brief

1 overview of the Division of Cytokine Biology and the Laboratory  
2 of Cellular Biology. There's going to be some slides that I have  
3 for the people on video. I will sort of read through it and I'll  
4 try not to spend too much time on the slides so that we can go  
5 ahead and get onto the discussion of the site visit report.

6 This just lists just some of the products that are  
7 being reviewed within the Division of Cytokine Biology.  
8 Basically what these consist of are predominantly all the  
9 interferons, which are interferon, alpha beta and gamma. We have  
10 some of the interleukins, which amount to interleukin 10 and  
11 interleukin 12. We also have some other soluble receptors, such  
12 as soluble TNF receptors, soluble IL4 receptors. We also have  
13 some products such as ICAM-1, and some soluble complement  
14 receptors.

15 These products are being used for a variety of  
16 indications which I don't think we need to get to at this point  
17 in time, but I at least wanted to give you a background in terms  
18 of just some of the products that are being reviewed in the  
19 division at this time.

20 The Laboratory of Cell Biology is looking at another  
21 set of products. If we could have the next slide, it goes into  
22 these products, which basically are growth factors which can be  
23 divided into the epidermal and the mesenchymal growth factors,  
24 which are products such as PBGF, EGF, FGF, and then the  
25 neurotrophic factors such as brain derived neurotrophic factor,

gileal derived neurotrophic factor, nerve growth factor, and NT3 and MGF, which summarizes basically most of the products that are under review in the Laboratory of Cell Biology.

4 The next slide just lists some of the indications for some of these products that are being reviewed in cell biology, which mainly focus on things like malignancy, mucosides, periodontal disease and cutaneous ulcerations.

8 Then some of the neurotrophic factors are being used for Parkinson's disease, myotrophic lateral sclerosis, peripheral neuropathy, multiple sclerosis, and some of the angiogenic factors are being used for myocardia revascularization.

12 I think we can probably just skip that slide. Okay. I just want to make a note that I made before, that all the scientists are part of what we think of as a review scientists program, where half of the time is being spent on scientific endeavors, which are basically outlined in the package that everyone has received, and review work which focuses on reviewing product license applications which are, as you are very well aware of, and INDs, which are predominantly most of what they are spending -- what they are predominantly spending most of their time on.

22 The INDs are focusing on the neurotrophic factors which I mentioned before, and a lot of the epidermal and mesenchymal factors which are very early in their product development.

25 Okay, you can go onto the next slide. I just wanted to

spend a couple minutes sort of relating the scientific research with the sort of the regulatory aspect of their career. The problem is, I can't read that slide from here. I thought that was better focused before.

5 Now I can read it. This is just something that comes out of the CFR. I just want to bring it up. What it says is to obtain a license for a product, the manufacturer shall submit data that meet prescribed standards of safety, purity, and potency.

10 I want to bring out the point safety, purity and potency, because I think these are aspects of any evaluation that are going to be evaluated by the scientists at CBER. I mean these are points of any sort of research program that deal with signal transduction pathways, animal models of safety and efficacy, and studies that deal with how products induce certain genes within a number of different cells.

17 I think that sort of summarizes much of the work that is being done by the five individuals that were part of the site visit team.

20 I want to just go into sort of briefly each of the members and sort of outline just in one or two sentences how I think that their particular work relates to these particular aspects of safety, purity, and potency. Then I think we can open up the discussion.

25 The work of Dr. Stromburg and Pegues have been dealing

with ovarian carcinoma. They have been looking at the function of erb B-2 and ligands binding to erb B-2. In relationship to that, there are several INDs within OTRR that look at monoclonal antibodies that are directed against erb B-2, that are used in malignant models.

6 I think it's clear that work that come out of that lab clearly has impact on how these INDs are evaluated.

8 It also has broader impact into how we evaluate all soluble receptor products, because these are -- many products that are being used to block the effects of cytokines on cells in terms of preventing these cytokines from eliciting certain biological effects.

13 The work of Dr. Johnson is focused on signal transduction, mainly using molecules such as EGF and PDGF and amphiregulin. This work again, is focused on one, at the receptor level looking at what other molecules are involved in terms of binding of the ligand to the receptor, how these molecules could potentially be modulated, either down-modulated or affected in terms of binding which would lead to changes in the overall responsiveness of the cell.

21 Then he's gone on to say there are other aspects of signal transduction within the cell that can effectively determine whether the cell will respond in a normal or abnormal way, which clearly gets into issues regarding the bioassays and how we evaluate any number of bioassays with these particular

growth factors.

2 The work of Dr. Wilcox clearly gets into issues of  
3 safety and efficacy on a number of neurotrophic factors, in  
4 particular with several animal models that deal with both motor  
5 neurons and sensoring neurons in terms of looking at long-term  
6 safety and efficacy of neurotrophic factors that we're currently  
7 regulating within the division now.

8 Finally, Dr. Fink, who is also looking at a number of  
9 signal transduction pathways within the neurotrophic area.  
10 Again, looking at aspects of how smaller molecules may affect how  
11 larger trophic factors can bind to receptors, how smaller  
12 molecules such as dexamethasone can effect the expression of  
13 receptors and lead to differences in the overall effect of  
14 neurotrophic factors on the cells.

15 So I think we have a number of scientists within this  
16 division who are clearly working on a group of sort of related  
17 but diverse aspects of within the Division of Cell Biology that  
18 clearly interact with a number of regulatory issues that we're  
19 dealing with pretty much on a daily to weekly basis with the INDS  
20 and DLAs that we're reviewing.

21 So I'll sort of finish my introduction with that. If  
22 there are any questions, I'll entertain any questions. I think  
23 we can go on.

24 DR. FREAS: Are there questions for Dr. Finbloom at  
25 this time?

1        Let me remind you, we are still in open session. We  
will2 have a closed session in a few minutes. But during this  
open3 session, not only is Dr. Finbloom here, but all the  
resear4 chers being reviewed are in the room. If you have  
questi5 ons for any of the researchers regarding their project or  
anybo6 dy here that you would like to discuss in open session, we  
welcom7 e your questions.

8        Dr. Vose, do you think at this time we should go into  
closed9 session, and maybe ask the people to stick around for 10  
to 15 minutes in case something comes up that we would want to  
call1 them back and address -- have them answer the question and  
proce2 d in closed session?

13       CHAIRPERSON VOSE: Yes. Why don't we proceed to closed  
sessi4 on, and have Dr. Kleinerman give a report, but ask them to  
stid5 e around for about 15 minutes. That would be great.

16       DR. FREAS: That's very good. Dr. Kleinerman, are you  
about17 ready? It will take us about two minutes to clear the  
room18 and we'll give you the go ahead if you are still there,  
whid19 I hope you are.

20       DR. KLEINERMAN: Yes. I am here. I am ready when you  
are21

22       DR. FREAS: Can everybody hear Dr. Kleinerman,  
ever23 ybody on the video hear Dr. Kleinerman. Okay, great.

24       (Whereupon, the meeting immediately reconvened in  
Clos25 ed Session.)

