

FOOD AND DRUG ADMINISTRATION
CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

FIFTY-FOURTH MEETING
OF THE
BLOOD PRODUCTS ADVISORY COMMITTEE

8:32 a.m.
Friday, March 14, 1997

Potomac Rooms I, II and III
Quality Suites Hotel

3 Research Court
Rockville, Maryland 20850

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P R O C E E D I N G S

(8:32 a.m.)

1
2
3 DR. SMALLWOOD: Good morning. I'd like to call
4 the session to order at this time.

5 This is the second day of the 54th meeting of
6 the Blood Products Advisory Committee. I'm Linda
7 Smallwood, the Executive Secretary.

8 Yesterday I read the conflict of interest
9 statement. That statement applies to today's proceedings
10 as well.

11 I would just like to make a brief announcement.
12 For those of you who are interested, the Public Health
13 Service Advisory Committee on Blood Safety and Availability
14 was scheduled to meet on March 20th and 21st. That meeting
15 has been postponed until a later date in April. There will
16 be a Federal Register notice announcing that.

17 DR. McCURDY: It's April 24th and 25th,
18 Thursday and Friday.

19 DR. SMALLWOOD: Thank you.

20 We have one agenda item this morning, the final
21 report of the site visit, Laboratory of Plasma Derivatives,
22 and Dr. Scott Swisher, the committee Chair, will preside
23 over these proceedings. Dr. Swisher.

24 DR. SWISHER: Good morning.

1 To get us started this morning, the
2 introductory remarks will be made by Dr. John Finlayson,
3 who is Associate Director of Science for the Office of
4 Blood Research and Review. John?

5 DR. FINLAYSON: Thank you, Dr. Swisher, and
6 good morning. I appreciate everyone coming out on a rainy
7 morning for these festivities.

8 As I was preparing some remarks for this, I was
9 sort of writing it as a multiple choice talk because if Dr.
10 Neil Goldman, who is the Associate Director for Research
11 for the entire Center of Biologics Evaluation and Research,
12 had showed up and wanted to make some remarks about the
13 research program at CBER, then what I was going to do was
14 simply be the transitional statement between Dr. Goldman
15 and Dr. Golding. So, I was reminding myself, don't make
16 any bad puns about all that glitters and so forth.

17 (Laughter.)

18 DR. FINLAYSON: Dr. Goldman is here and he is
19 lurking in the back of the room, but he said I should go
20 ahead and tell what I think he might have said, albeit it
21 I'm sure not in the glorious detail that he would have
22 given it in, and then do something to segue into Dr.
23 Golding's presentation, which is really the thing that
24 you're here to listen to.

1 I therefore want to do several things here in
2 my opening remarks. If we can see the first slide. It may
3 not be visible to the folks in the back of the room, but I
4 hope it's visible to the committee.

5 The first item I've written there is, why do
6 research in CBER? I realize this sounds like it's going to
7 be the beginning of a sermon to the choir, but at the same
8 time, having spent so many years of my life in truth-in-
9 labeling, that I figure if I'm going to say anything about
10 it at all, I could at least give you my perception of the
11 answer to the question.

12 The other reason I bring it up is it's a
13 question that's being asked with increasing frequency in a
14 number of quarters, and I think we're obligated to say a
15 little something about it.

16 I also want to say something about current and
17 proposed developments in CBER research and then say
18 something about developments that have already occurred in
19 the Office of Blood Research and Review in terms of the
20 research program.

21 I will reiterate the tasks that the Blood
22 Products Advisory Committee has before it this morning.

23 Then I will address some, but only some, of the
24 issues raised by the site visit team.

1 The others will be addressed by Dr. Golding in
2 his presentation.

3 Then I'll give you a quick overview of the
4 Office of Blood Research and Review just to show you its
5 component parts and then I will introduce Dr. Golding's
6 presentation and by that time I hope there will be a little
7 time left to give his presentation.

8 Why do research in CBER? Well, as I said, this
9 has been asked many times over the decades, but in the last
10 year or two it's being asked with a great deal more
11 frequency, and I might say with a great deal more volume.
12 This is for some reasons that I'll talk about in just a few
13 moments.

14 As a result, each of the offices that have
15 laboratories in the Center for Biologics Evaluation and
16 Research has done a great deal of soul-searching and head-
17 scratching to come up with some answers to this. Each of
18 the offices has come up with its own thoughts, and as a
19 result of this, many words have been written. But for me,
20 a picture is worth a thousand words. I'm not going to show
21 you the picture because it would take me a great deal of
22 effort to find it, but I'm going to tell you about it.

23 The picture is one that I saw in an
24 advertisement more than half a century ago. It showed a

1 group of gentlemen in the drab clothing of the merchant
2 class of the 19th century, and they were gathered around a
3 seated figure who was dressed very much the same way except
4 that he seemed to be wearing sort of a black skull cap. He
5 was listening intently to what these gentlemen were
6 saying, and their faces seemed to reflect a great deal of
7 concern. The caption was, "Messr. Pasteur, why does our
8 wine sour?"

9 I don't have to tell this audience of all of
10 the fundamental discoveries that Louis Pasteur made in
11 trying to answer this very practical commercial question.
12 Nor do I have to tell this audience about all of the many
13 practical applications that came out of his fundamental
14 observations.

15 But the point emerging from this I think is
16 that this road from the practical question to the
17 fundamental observation runs in both directions, and a CBER
18 scientist should not only be willing but able to walk in
19 either direction as the situation calls for it. CBER is
20 literally confronted with dozens of practical questions all
21 the time and has to be prepared to develop the information
22 to respond to them. What we would ideally like to do would
23 be to develop information that would actually allow us to
24 anticipate questions like this.

1 Let's go to the next overhead. I've titled
2 this Proposed Developments in CBER Research, but actually
3 some of these have already taken place.

4 This is one of the elements that has emerged
5 from CBER's strategic plan, and yes, we have strategic
6 plans just like everybody else and they follow a script
7 just like in Dilbert just like everybody else. So, this is
8 selected because, of course, the strategic plan is very
9 long. It fills up a whole notebook, and even the strategic
10 plan having to do with research is considerably longer than
11 this.

12 But one of the developments that the strategic
13 plan calls for is the development of a coordinated model of
14 research driven by regulatory need.

15 Another is the implementation of a procedure
16 for determining the allocation of resources, if in fact it
17 turns out there are any resources to allocate, and then to
18 establish a CBER research advisory committee.

19 To bring you up to date, I'd like to take the
20 next overhead to say a little something about this CBER
21 research advisory committee which does not yet exist but
22 which work is underway to constitute.

23 The idea is that it would be drawn from
24 currently extant advisory committees, other government

1 agencies, academic institutions, and industry. Its initial
2 task would be to perform a global -- and I say
3 retrospective, which means simply as it exists now --
4 review of the CBER research program and then to evaluate
5 proposed future CBER research. The membership and the
6 details are still to be worked out and the actual mechanism
7 of action is still to be worked out, but I wanted to
8 apprise you of the fact that this is one of the
9 developments that is coming.

10 One of the driving forces in the asking of the
11 question of why do research in CBER has certainly been the
12 PDUFA funds. Now, notice that subtle change that took
13 place there. I went from a four-letter code like CBER and
14 OBRR to a five-letter code, PDUFA, P-D-U-F-A,
15 Pharmaceutical Drug User Fee Act. This is legislation
16 which went into effect five years ago under which the
17 pharmaceutical manufacturers would pay user fees for the
18 review of applications which came in. This was given a
19 finite life span which was give years. Since it went into
20 effect in 1992, we are coming to the end of that. So,
21 legislation is pending to decide what form PDUFA will take
22 for the future. It could be renewed more or less in its
23 present form. It could provide more funds for review
24 purposes, or of course it could sunset.

1 But one thing that manufacturing umbrella
2 groups have been adamant about is that PDUFA funds should
3 not be used in the support of research. This is, of
4 course, going to mean, regardless of how we put filigree on
5 it, that the de facto funds available for research are
6 going to decrease within CBER. So, a request was made that
7 those responsible for research in CBER see that the
8 research programs are prioritized.

9 To date this has not been done on a CBER-wide
10 basis. This has been done on an office-wide basis; that
11 is, the Office of Blood Research and Review, the Office of
12 Therapeutics Research and Review, the Office of Vaccine
13 Research and Review have each developed its own model for
14 prioritization.

15 Now, in the Office of Blood Research and
16 Review, we did not develop a numerical rating; that is, we
17 did not emerge saying, for example, that platelet research
18 is more important than research on viral safety of plasma
19 derivatives but less important than standardization of new
20 clotting factors. That we did not do. What we did say was
21 that only those consolidated core programs that met certain
22 criteria, which I will show you in a minute, were to be
23 continued.

24 Now, we are all, in whatever organization we

1 work for, confronted with exercises like this from time to
2 time. Of course, we being dutiful employees perform them.
3 The question is always, did it have any effect? I think in
4 the case of this exercise in the Office of Blood Research
5 and Review there was a measurable effect. In fact, I think
6 there were two measurable effects.

7 One was emergent from the fact that for
8 reporting purposes, every research project in CBER gets a
9 serial number, and these serial numbers are used when we
10 write our annual report and these serial numbers have been
11 used when, for a two-week period out of every quarter, we
12 are supposed to report what we do with our time on an hour-
13 by-hour, minute-by-minute through the day. So, if someone
14 is working on a particular research project, he or she can
15 key it to that serial number of research projects.

16 So, what I was able to do was to go back over
17 the period that PDUFA has been in effect, that is, 1992
18 through 1996, inclusive, and simply count the number of
19 extant research projects and compare that with the number
20 that have ever been extant in that period. It turns out
21 that in the Office of Blood Research and Review, of the 88
22 projects that have existed during that time, only 27
23 existed after the prioritization.

24 Now, did all of them disappear because of

1 prioritization? Did all of those 61 disappear because of
2 prioritization? No. However, I think there was an impact
3 there.

4 The disappearance, if you will, I was able to
5 categorize, and I have not taken the time to prepare
6 quantitative figures for this, but they disappeared for a
7 number of reasons.

8 One is, believe it or not, some of the projects
9 were actually completed. I found this astounding, but in
10 the midst of regulatory chaos, some research scientists
11 were actually able to have a beginning, a middle, and an
12 end to research projects.

13 In many instances, researchers who, of course
14 like all researchers in CBER, also had review
15 responsibilities in the regulatory program, became full-
16 time reviewers and the project or projects that that person
17 was working on were not continued.

18 There were, in the course of review -- and I
19 mean review of the research program now, not regulatory
20 review -- a number of projects which were found to be
21 either unproductive or not meeting these criteria that I
22 will show you and were therefore simply terminated.

23 There were others that were consolidated with
24 other programs and probably a major factor was when the

1 unproductive parts of individual projects were lopped off
2 and terminated and the relevant parts, the ones that met
3 the criteria, were folded into extant other projects.

4 I mentioned that there was a second effect, at
5 least in the Office of Blood Research and Review, of this
6 prioritization, and that was that going through this
7 exercise let us see areas that were not being addressed on
8 a research basis. The most notable of those in the Office
9 of Blood Research and Review was that we saw we were not
10 doing any laboratory research on bacterial and parasitic
11 contamination of blood. So, we were able to hire Dr.
12 Walter Koch in the Division of Transfusion Transmitted
13 Diseases to begin setting up such a program.

14 So, thus, as of the end of last calendar year,
15 if we look at the next overhead, we can see what the
16 consolidated core programs looked like. I won't spend much
17 time on this, but you'll see that in the Division of
18 Hematology, they sorted out to these three areas that we
19 felt these are the things we really ought to have a
20 research program going on: blood cells and cell-derived
21 proteins, coagulant proteins and their analogs, and non-
22 coagulant plasma derivatives and their analogs.

23 In the Division of Transfusion Transmitted
24 Diseases, you can see that it sorted out along the lines of

1 the infectious agents, retroviruses, hepatitis viruses, and
2 this new endeavor in bacterial and parasitic contamination.

3 What were the explicit criteria or roles of
4 research in OBRR that emerged? We see that the feeling was
5 that the role of research in the blood program is to
6 address existing safety and efficacy issues; address
7 unexpected product events at a scientific level, for
8 example, the Gammagard incident that many of you have heard
9 a great deal about; to assess new threats to the blood
10 supply and new threats to blood products; to assess new
11 products and new alternatives, meaning new therapeutic or
12 diagnostic or prophylactic alternatives; to support
13 regulatory control, be it regulatory control of products,
14 for example, in the lot release program; or support
15 regulation in the sense of policy development if one is
16 going to promulgate a policy and needs information to
17 underlie that policy; and then finally, something that we
18 think is very important, to support cross-cutting
19 activities related to other CBER programs outside of the
20 Office of Blood Research and Review, but in which our
21 scientists are called upon to offer their expertise.

22 Was this all? No. There were some implicit
23 criteria underlying that. A given research program would
24 not necessarily have to meet all of the criteria on the

1 previous slide, but all of them would certainly have to
2 meet the first one on this slide: quality and excellence.
3 If it was not of quality, if it was not excellent, we just
4 shouldn't be doing it. We couldn't afford to be doing it.

5 Another implicit criterion was it addressing
6 unique needs or making use of unique abilities of the
7 Office of Blood Research and Review and CBER.

8 Then does it have potential public health
9 impact.

10 With that in mind, what do we want you to do
11 for us? Traditionally, I have asked site visit teams and,
12 by extension, the advisory committee to do the following:
13 one, to evaluate the quality of the research that the site
14 visit team is seeing, to evaluate its relevance to the
15 regulatory program that that group is responsible for, and
16 to evaluate individual scientists.

17 Now, these are still valid tasks, but we have
18 broadened the second one there so that relevance has been
19 extended to what I'll call appropriateness. Is the
20 direction of the research suitable? Is the emphasis
21 appropriate and so forth?

22 Today Dr. Golding is going to give you an
23 overview of the Laboratory of Plasma Derivatives. After
24 final discussions, you will be asked to come up with a

1 final report which will embody these three areas. Now,
2 there are five individual scientists mentioned in the draft
3 report, which you have. Dr. Andrew Shrake, who is a
4 permanent staff member, is being evaluated for the
5 continuing of his research program. Dr. Golding and Dr. Yu
6 are being evaluated for promotion.

7 Dr. Yu called me up last night. She had just
8 returned from a meeting on hepatitis C in Japan, and she
9 was feeling very much under the weather. Fortunately, she
10 didn't get hepatitis C from her trip, but she will not be
11 with us today.

12 Dr. Dorothy Scott is another of the scientists
13 mentioned in your package. Dr. Scott has been here for a
14 little over three and a half years, so she is, in essence,
15 midway in the classical CBER staff fellowship program, and
16 the question you are being asked is, is she on track for
17 potential conversion to permanent status over the next
18 three to three and a half years?

19 Dr. Suong Tran has been here only a little a
20 year and a half, and the question being asked with respect
21 to her research is, is she on the right track?

22 Obviously discussion of individual scientists
23 is to be done in the closed session, but the overall
24 research program can be done in the open session.

1 I wanted to talk about some of the issues
2 raised by the site visit team. You have all received the
3 draft report and you saw that the site visit team's
4 discussion was quite wide-ranging, which I think is a good
5 thing.

6 Among the points that were raised was the
7 overall organization of research throughout CBER, that is,
8 the organization of research through the entire Center for
9 Biologics Evaluation and Research. With respect to that, I
10 would say it's probably too much to expect the scientists
11 in the Laboratory of Plasma Derivatives to shoulder the
12 responsibility for how the entire Center's research program
13 is organized. I can also say that this is an issue that
14 will surely be addressed by the CBER research advisory
15 committee. But I also say that since it's in the current
16 draft, I should say something about it.

17 Now, the site visit team's commentary,
18 evaluation if you will, of the organization of CBER
19 research focused about the fact that it is product
20 centered. For that research with its product centered
21 organization, they placed it on a scale of between
22 suboptimal and dysfunctional.

23 Now, at the outset I want to spell out several
24 things. First, this is not a problem that we expect you to

1 solve today. Secondly, I do not want what I say to be
2 taken as discounting in any way the very cogent
3 observations that the site visit team made about
4 organization of research teams to solve problems because I
5 think they had some very good ideas there.

6 I also recognize that in 1997 anybody that says
7 anything that even sounds like it is arguing against large
8 scale change is going to hear a crescendo of, oh, yeah,
9 business as usual, defending the status quo. But I do want
10 to point out some features of the product orientation that
11 has been the focus of research in the past that I think we
12 should make an effort not to lose in our effort to do good
13 in any reorganization that we might undertake. Certainly I
14 want to couch these remarks in terms of rationality not
15 just simply stodginess, we've always done it that way.

16 Now, having given that little introduction, I
17 would like to express my thoughts in some very original
18 words. Unfortunately, the words were already spoken about
19 two years before I was born, and those of you who have
20 medical degrees probably are familiar with the name of the
21 gentleman who spoke them. If you went to medical school,
22 you probably at least read about and maybe even did an
23 Addis count. I'm looking for flickers of recognition.
24 Yes. As I recall, you counted the cells in 10 milliliters

1 of urinary sediment and then you went through a calculation
2 to see how many cells were shed from the urogenital tract
3 in a 12-hour period.

4 The Addis count as named after Thomas Addis who
5 was a Scotsman who migrated to southern California and in
6 southern California had a long and distinguished career as
7 a renal physiologist.

8 In the first third of the century, he was
9 giving a talk to the California Academy of Medicine, and he
10 was speaking to a group of physicians. He was rather tough
11 on them. Very early in his talk, he says, the medieval
12 physician at least looked at his patient's urine. Now a
13 urine sample is whisked off to the clinical laboratory and
14 put into the capable hands of a chemist and the chemist
15 analyzes it and the chemist does any necessary calculations
16 and the chemist writes a report on it and then the chemist
17 delivers this report into the hands of the physician. Then
18 likely as not, the chemist will have to interpret what it
19 means for the physician and will even given the physician
20 the language, the nomenclature, in which to discuss the
21 results. Then he sort of says, but the physician will
22 probably ignore this nomenclature anyway and use whatever
23 nomenclature was learned in medical school. He goes on and
24 on like this.

1 So, he says, given all this, is there any place
2 for the physician in research? And he answers
3 resoundingly, yes. But how, in view of all of that, can
4 this be? Because, said Professor Addis, the physician is
5 in the position to ask the right questions.

6 So, it occurs to me that if you have a group of
7 people who day after day after day are faced with the down-
8 to-earth, practical regulatory problems -- and bear in
9 mind, "regulatory" covers a lot of ground. It's not all
10 recalls and patient notification. "Regulatory" covers
11 product effectiveness, adverse reactions, testing,
12 manufacturing, stability, mechanism of action. If you have
13 a group of people who are day after day thinking about the
14 regulatory problems about a class of products, it is not
15 unreasonable to expect that those people might be in the
16 position to ask the right questions about those products.

17 Furthermore, if we think about this, it might
18 not be unreasonable to expect that if you have a group of
19 people -- and I will use the Laboratory of Plasma
20 Derivatives as the example -- who have diverse backgrounds,
21 a physical chemist, a pharmacologist, an immunologist, that
22 in their thinking day after day about these products, they
23 might be in a position not only to ask the right questions,
24 but to bring their diverse backgrounds to bear in solving

1 them, and if they find that they don't have the expertise
2 themselves, by their very diversity, to have a network
3 among colleagues informally to bring in other expertise
4 faster than one might get it through a formal structure.

5 Now, with that in mind, why don't we talk about
6 the organization administratively of CBER, and let me give
7 a handout at the same time.

8 Now, let's look at the first slide. This is a
9 ridiculously busy slide. Of course, CBER is a ridiculously
10 busy organization. But you will see that it starts off up
11 here with the Director and the Director's immediate office.
12 It has a number of sidebars here and then you see the
13 individual offices here.

14 I might also point out that almost by
15 definition the slide is not accurate. You will see up here
16 under Dr. Zoon's name, there is an empty space for the
17 Deputy Director, Mark Ellengold, whom you met yesterday,
18 has moved over here as acting Deputy Director. You see,
19 when this was made up last summer, it was so new that Dr.
20 Goldman had to be written in by hand. I see up here Frank
21 Claunts has moved to another part of the FDA and there is
22 an acting Director of the Office of Management.

23 But it's over here that we are going to be
24 talking about. This is the Office of Blood Research and

1 Review, and these are the five offices across here that are
2 our functional units. The three in the middle Office of
3 Blood Research and Review, Office of Therapeutics Research
4 and Review, and Office of Vaccine Research and Review, are
5 the ones that are heavily laboratory oriented although
6 laboratories do exist in the Office of Establishment,
7 Licensing and Product Surveillance.

8 If we look at the next one, these are the
9 offices that we have. Office of Establishment, Licensing
10 and Product Surveillance. These people, as the name
11 implies, are responsible for the review of the actual
12 physical establishment layouts, air, water, earth, fire,
13 and so forth, as well as in the lot release program. It is
14 this group to which the samples are originally submitted by
15 the manufacturers and back from which the release to the
16 manufacturer goes.

17 The Office of Compliance is just what it sounds
18 like. These are the enforcement people and the people who
19 oversee recalls.

20 Office of Therapeutics Research and Review is
21 heavily directed to recombinant DNA products, but by no
22 means exclusively because monoclonal antibodies are dealt
23 with in this office and a wide ranging group of things such
24 as gene therapy.

1 Office of Vaccine Research and Review is just
2 what it sounds like, but even it has its own niches of
3 diversity. For example, allergenic products live in this
4 group.

5 Let's expand this by going to the next
6 overhead. This is the Office of Blood Research and Review.
7 Jay Epstein is the Director. You see there's an empty
8 space left in here. That's because that's where I live.
9 Actually it's because until Wednesday of this week, I never
10 used Power Point so I don't quite have the range on it yet.
11 But also in this empty space lives the tissue program.

12 If we look at the divisions, which is the next
13 organizational unit down, you met each of these people
14 yesterday. Each of them made a presentation. Mark
15 Weinstein is the acting Director of the Division of
16 Hematology. Ed Tabor is the Director of the Division of
17 Transfusion Transmitted Diseases and Mary Gustafson is the
18 Director of the Division of Blood Applications. This is
19 our initial regulatory review unit and our administrative
20 unit. When a manufacturer makes a submission, it comes
21 into this group, and when a license is issued, it is issued
22 from this group.

23 In addition to that, however, the Division of
24 Blood Applications is the reviewer for the traditional

1 blood bank products, whole blood, red cells, plasma for
2 transfusion, and plasma as starting material for further
3 manufacture

4 In addition, there is a little bit of
5 laboratory research -- well, I should say laboratory
6 activity -- that goes on in this group because the release
7 testing, when it is done, of blood grouping and typing
8 reagents is under this group.

9 Dr. Tabor's group, as you well know, is
10 responsible for the serological test kits and, of course,
11 for the nucleic acid based diagnostic tests as well.

12 Let's expand this by going to the next slide.
13 You see there's an empty space under Mark Weinstein.
14 That's because Dr. Weinstein is the Deputy Director of the
15 Division of Hematology, but he's also the acting Director
16 of the Division of Hematology. So, he's sort of his own
17 boss and his own subordinate, and that continues down here
18 because I'm not sure whether he's Chief or acting Chief of
19 the Laboratory of Hemostasis. But once he moved up to
20 become Deputy Director, this position was never filled.
21 So, you see, he's got all these three hats going down here.
22 That keeps him occupied between Friday afternoon blood
23 crises, as he mentioned to you.

24 Dr. Harvath is the Chief of the Laboratory of

1 Cellular Hemostasis. This is the laboratory which is
2 responsible for platelets, for white cells. We do not have
3 a research program on red blood cells, but if it existed,
4 it would be in this group. We have the next best thing,
5 though. We have a research program on hemoglobin solutions
6 and a number of you have met Dr. Alayash who is in charge
7 of that program.

8 Dr. Golding is the acting Chief of the
9 Laboratory of Plasma Derivatives, and he will elaborate
10 further upon this. Dr. Golding became acting Chief of the
11 Laboratory of Plasma Derivatives after Don Tankersley, whom
12 I think you all know, left in November of 1995. Dr.
13 Weinstein became acting Director of the Division of
14 Hematology with the departure of Dr. Joseph Frattoni who
15 left in November of 1996. Maybe T.S. Elliott was wrong.
16 Maybe November is the cruelest month.

17 Anyway, this seems to be a good starting point
18 for Dr. Golding. I have actually asked Dr. Golding to do
19 four things, not necessarily in the order that I will
20 mention them here. I've asked him to describe the
21 regulatory responsibilities of the Laboratory of Plasma
22 Derivatives. I've asked him to tell you about the
23 structure and substructure of the laboratory. I've, of
24 course, asked him to give an overview of the research

1 program because this is a major thing that you're here to
2 hear this morning, and I have asked him to tell about the
3 relevance of the laboratory's research program to its
4 regulatory program.

5 In the course of the latter, I have asked him
6 to address an issue that was raised in the draft site visit
7 report which is the relationship of his own work and that
8 of Dr. Dorothy Scott to, first, the mission of the Office
9 of Blood Research and Review and then, second, to the
10 explicit research criteria that I showed you earlier.

11 I think, unless there are specific questions
12 for me, I will stop there and turn the podium over to Dr.
13 Swisher and/or Dr. Golding.

14 DR. SWISHER: Are there questions for Dr.
15 Finlayson now? He will be available to us for the
16 remainder of the morning.

17 (No response.)

18 DR. SWISHER: If not, Dr. Golding, would you
19 like to go ahead and take over?

20 DR. GOLDING: Good morning. I value this
21 opportunity to present to the Blood Products Advisory
22 Committee the activities of the Laboratory of Plasma
23 Derivatives, both in terms of the regulatory work and in
24 terms of the research that is performed in the laboratory.

1 This is not an easy task for me. As Dr.
2 Finlayson mentioned, I became the acting lab chief in
3 November of 1995, and I hope what I do today does reflect
4 the dedication and hard work of the people that work in the
5 Laboratory of Plasma Derivatives, some of whom have been
6 there for 15 years or more.

7 The organization of the Laboratory of Plasma
8 Derivatives is essentially as you see on the slide with
9 myself as the acting lab chief. Andrew Shrake is the
10 section head of physical biochemistry; Mei-ying Yu, the
11 section head of viral safety; and myself, the section head
12 of immunology.

13 In the site visit, as was mentioned by Dr.
14 Finlayson, the site visit team were asked to evaluate the
15 work of Dr. Shrake, to evaluate the work and consider
16 promotion of Drs. Mei-ying Yu and myself, and to consider
17 the staff fellows, Suong Tran and Dorothy Scott, as
18 candidates to be converted to more permanent positions.
19 Suong Tran at the time had only been in the lab for about a
20 year, and Dorothy Scott has been in my lab for three years.

21 Going through each section, Dr. Shrake is the
22 section head of physical biochemistry. He joined the group
23 in 1980. Suong Tran joined just more than a year ago. The
24 Section of Viral Safety, Dr. Yu is the section head. She

1 also joined the group more than 15 years ago, and she has
2 added to her group Paula Hines quite recently. Dr. Guo has
3 been there since 1992 as a Fogarty fellow. He's now an
4 ORISE fellow. Bobby Mason is a microbiologist. He has
5 been in the lab for a long time. Julia Jong is a more
6 recent addition and works there as a biologist.

7 In the Immunology Section, myself as the
8 section head. Dr. Scott joined in 1993. Then we have Lee
9 Stevan since 1980. Coty Huang is a biologist who recently
10 joined our group. Inna Agranovich is a Fogarty fellow, has
11 been with us for a couple of years now. And these two
12 ORISE fellows. The funding for these two fellows actually
13 has come from grants that we've been able to generate from
14 our own research. These are competitive grants that we
15 receive through the Office of Women's Health and through
16 the NIH intramural program. Doug Frazier is a regulatory
17 assistant who also works in the laboratory.

18 What are the products that we regulate? Well,
19 we have some volume expanders. The albumin and plasma
20 protein fraction, the hetastarch, the pentastarch, the
21 Dextran 40 and Dextran 70, all fit into this group of
22 volume expanders.

23 Alpha-1 proteinase inhibitor is a relatively
24 new addition to the products that we regulate. This

1 inhibitor inhibits elastases, important in preventing
2 tissue destruction in people who have a deficiency.

3 As I'm sure you're all aware, we also regulate
4 immune globulins, intravenous and intramuscular, and these
5 come in two forms: general immunoglobulins and hyper-
6 immune immunoglobulins that are specific for particular
7 infectious diseases.

8 So, the research is divided up generally into
9 these sections. The physical and biochemical
10 characterization of plasma derivatives and related proteins
11 and materials in Dr. Shrake's group, studies related to
12 viral safety of plasma-derived products in Dr. Yu's group,
13 and development of an anti-HIV therapeutic vaccine looking
14 particularly at Ig class and subclass responses, and also
15 studies of cytokine regulation in human and murine immune
16 responses. These two projects are in my section, in the
17 immunology section.

18 So, just going through the different
19 investigators and trying to highlight some of the
20 regulatory and research activities, I'm involved very
21 recently with the albumin recall due to bacterial
22 contamination of an albumin product.

23 I was involved in a task force that was asked
24 to have in place adequate supplies of botulinum immune

1 globulin in case of an emergency situation at the Olympic
2 Games. This involved actually writing an emergency IND and
3 providing it for CDC that they could use this in that
4 situation.

5 Shortly after joining the group, I was asked to
6 be the chairperson of a product license application for
7 pediatric AIDS using IVIG.

8 I've mentioned the grant awards that we have
9 received. I've been invited to national and international
10 meetings to present my work. At the FDA I'm involved in
11 grant review. These are study sections reviewing grants
12 for these types of organizations, and I'm also involved in
13 the strategic planing committee for promotion and tenure
14 and recruitment.

15 Dr. Scott, shortly after she arrived on the
16 scene at the FDA, was asked to be the medical reviewer for
17 a product license application, RSV, respiratory syncytial
18 virus, immunoglobulin, and she presented this review to the
19 BPAC committee. Her research is involved in setting up an
20 allergic model studying both basic and applied mechanisms.
21 She's also involved as a reviewer on study sections. She's
22 a reviewer for the Journal of Immunology. As far as
23 administration and policy is concerned, she's a member of
24 the NIH/NIAMS Institutional Review Board. She's also a

1 member of the Committee for the Advancement of Science at
2 CBER and is an active member of the Rheumatology Working
3 Group at the FDA.

4 Dr. Yu has been working on viral safety issues,
5 particularly HCV. She set up the assay. She has trained
6 people from industry. People in her lab and herself have
7 improved the procedure so that it can be used for lot
8 release testing. She's also involved from a regulatory
9 point of view in looking at product quality and stability.
10 Particular products that she looks at are the albumin and
11 immune globulins.

12 She played a very critical role with the
13 albumin recall situation where she was one of the first
14 inspectors on the scene and made critical findings which
15 helped us understand how the albumin got contaminated.

16 Her research is involving the mechanisms
17 involved in HCV transmission, expression and
18 characterization of HCV envelope proteins, and she has been
19 invited as a speaker to both national and international
20 meetings.

21 In terms of administration and policy, she has
22 helped to write documents for the International Committee
23 on Harmonization at the FDA and has played a very active
24 role in getting recommendation letters out to industry,

1 especially regarding viral validation and viral removal
2 steps that are required to ensure the safety of these
3 products.

4 Dr. Shrake has been involved in the regulation
5 of albumin, and research in his lab provided the data that
6 allowed approval of a single stabilizer to be used in
7 albumin. Also research in his lab provided the basis for
8 using HPLC as a test for generic hetastarches.

9 Recently there was a recall of albumin because
10 of an incident of prekallikrein A activation levels rising
11 during the storage of the material. He went on an
12 inspection to the company and his findings have enabled us
13 to at least put forward a cogent hypothesis as to why this
14 occurred, and research is now being done in the lab to try
15 and define exactly what causes this increase in PKA with
16 storage of the albumin.

17 His research is related to looking at protein
18 stability and structure of proteins. He also performs
19 research looking at volume expanders, and this I'll discuss
20 in a little bit more detail later.

21 In terms of administration and policy, he's
22 also been involved in documents for the International
23 Committee on Harmonization and, very importantly, has
24 played a critical role in providing data for a monograph

1 which is to come out on Dextran 40 and Dextran 70, a USP
2 monograph.

3 Dr. Tran, who works under Dr. Shrake's
4 supervision, has been regulating alpha-1 proteinase
5 inhibitor and has been doing work in the lab to provide a
6 reference standard for the assay and has actually been
7 working on the assay to improve the potency assay. So, her
8 research is actually in the field of alpha-1 proteinase
9 inhibitor looking at protein folding and function.

10 In terms of administration and policy, she's a
11 member of the Research Subcommittee of the Information Data
12 Committee.

13 This is just to give you an idea of the types
14 of review work that we look at. We look at investigational
15 new drug applications, product license applications, and so
16 on. These are the numbers that we get over a single fiscal
17 year. I'm not going to bore you with the actual hours it
18 takes to review these and show you how much time is taken
19 by the members of the lab in doing this actual review work.
20 This does not include pre-IND meetings, meetings that are
21 done at the pivotal stage of a biologic development, the
22 pre-pivotal study meetings that occur before the phase III
23 studies, and other meetings that occur formally and
24 informally with industry and within the FDA, but just to

1 give you some flavor of the workload that is involved in
2 reviewing these products.

3 So, the regulatory issues that we come up with
4 relate to standards for products, potency tests, the safety
5 of products, the mechanism of action, adverse effects, and
6 bioequivalence. So, I'm going to give you some examples
7 where the Laboratory of Plasma Derivatives has made some
8 inroads into solving these types of issues.

9 In the Laboratory of Plasma Derivatives, an Ig
10 lot number 176 was identified which is used by industry as
11 a standard for antibody titers against polio, measles, and
12 there are data available relating this standard to
13 hepatitis A and B titers.

14 Immunoglobulin lot number 2 was researched by
15 Dr. Yu's group and is used as a standard for HCV reverse
16 transcriptase PCR.

17 Another lot number 2 has been used for
18 standardization of the potency assay for hepatitis B immune
19 globulin.

20 As I mentioned, Dr. Suong Tran has been working
21 on standards for the alpha-1 proteinase inhibitor.

22 We also have a lot which is available for
23 industry for standardizing PKA testing of biologic
24 products.

1 In terms of potency -- I'll get into this in a
2 little bit more detail later, but Dr. Shrake's lab has
3 validated size exclusion chromatography HPLC for molecular
4 weight measurement which is important for plasma for
5 measuring volume expanders for the potency of volume
6 expanders.

7 I also mentioned that Dr. Tran is modifying and
8 improving the assay for detecting alpha-1 proteinase
9 inhibitor.

10 In Dr. Yu's lab, albumin and immune globulins
11 are monitored on a regular basis for molecular integrity by
12 HPLC, and they now incorporate capillary zone
13 electrophoresis for measuring these parameters.

14 In term of safety, I'll discuss this in more
15 detail later, but Dr. Yu's lab has been instrumental in
16 developing PCR assay for measuring HTV which is used widely
17 by industry and is a lot release test for any product that
18 is not treated with viral removal steps.

19 The PKA assay was recently resuscitated in our
20 lab after we became aware of a problem with PKA from one
21 company, and we're now using that as a lot release test for
22 that particular albumin product.

23 In terms of the mechanism of action, my lab is
24 looking at how to induce particular immunoglobulin classes

1 and subclasses, and we think this is important because
2 different classes and subclasses have different biologic
3 activities and it may be important in the future, for
4 example, in viral infections, to use an Ig subclass that is
5 more effective in clearing virus.

6 We're also looking into cytokines. This is
7 important probably in the mechanism of action of immune
8 globulins, but more importantly it's probably related to
9 the type of immune globulin you get in a particular
10 situation. We'll get into this later in the presentation.

11 In terms of adverse effects, again cytokines
12 have been implicated in adverse effects to plasma-derived
13 products, and I'll discuss this a little later. IgE-type
14 immediate hypersensitivity reactions, although rare, can
15 occur with immune globulin products particularly in
16 individuals which have selective IgA deficiency.

17 In terms of bioequivalence, I've already
18 mentioned that in Dr. Shrake's lab he has devised an HPLC
19 method that can be used to measure volume expanders. This
20 has been used by industry to show that their product has
21 bioequivalence with other products.

22 I've just covered very quickly the research
23 related to regulation and the regulatory issues that we
24 deal with in the Laboratory of Plasma Derivatives. I'm now

1 going to go into more detail into particular research
2 projects that we perform in the lab. I'm not going to have
3 time to discuss these by showing any data, but this will
4 mainly consist of summary slides, providing a title of the
5 project, the major findings, the conclusions, and as
6 mentioned by Dr. Finlayson, I'm going to try and indicate
7 how these projects are mission related and also indicate
8 what the future directions are.

9 So, the first project I'm going to discuss is a
10 project done under my supervision. The title of the
11 project is Development of an Immunotherapeutic Approach
12 against HIV 1. HIV infection, as you probably know, is
13 associated with a decrease in function and number of CD4 T
14 cells. These are the helper T cells. In order to bypass
15 this defect, a stimulus is required that can activate
16 effector cells, such as B cells, and cytotoxic T cells
17 directly because these cells require T cell help for most
18 immune responses.

19 The gram-negative intracellular bacteria
20 *Brucella abortus*, abbreviated BA, was tested as a candidate
21 for this purpose based on previous experiments showing that
22 TNP is a hapten conjugated to *Brucella abortus*, that these
23 conjugates could activate mouse and human B cells in a T-
24 independent manner so that you would not require T help and

1 you would still get responses.

2 So, HIV peptide, a small peptide from the V3
3 loop which is known to be a neutralizing determinant, was
4 coupled to Brucella and induced anti-peptide antibody
5 responses in normal mice and in mice lacking CD4 T cells.
6 These antibodies recognized the native form of the viral
7 envelope and were capable of neutralizing HIV 1 in vitro.
8 The major isotype elicited by the peptide BA conjugate was
9 IgG2a. So, this isotype is an isotype that is complement
10 fixing as has been shown in the mouse to be important as
11 having antiviral effects, and there is indication in the
12 human that the analogous immunoglobulin IgG3 has similar
13 effects.

14 Peptide BA was also capable of generating
15 cytotoxic T cell responses in normal mice and in mice
16 depleted of CD4 T cells. So, these mice were constructed
17 so they would lack T helper cells and would mimic the
18 situation that you get in HIV infection. These cytotoxic T
19 cells could lyse target cells expressing the native form of
20 HIV 1 envelope.

21 Mice and monkeys were immunized with peptide
22 Brucella, developed systemic and mucosal IgG and IgA
23 antibody responses against HIV 1 and mucosal samples were
24 able to neutralize HIV 1 in vitro.

1 Cytokine analysis of mice immunized with the
2 peptide BA revealed that Th1-like factors were induced,
3 namely IL-12 and interferon-gamma. Again, these cytokines
4 are known to be beneficial in certain intracellular
5 infections including viral and parasitic infections.
6 *Brucella abortus* was also shown to elicit Th1-like
7 cytokines from human cells.

8 Lipopolysaccharide was purified from *Brucella*
9 and shown to be several logs less toxic than
10 lipopolysaccharide from *E. coli*. Peptide conjugated to
11 this lipopolysaccharide was capable of eliciting
12 neutralizing anti-HIV 1 antibody responses in mice,
13 including IgA responses.

14 So, in conclusion peptide *Brucella abortus* can
15 bypass the requirement for CD4 T cells and stimulate B
16 cells and cytotoxic T cells that affect the cells directly.
17 This has implications for immunotherapy of HIV infected
18 persons against HIV 1 and also against other infectious
19 agents. So, it is possible to take peptides from other
20 organisms, conjugate them to *Brucella* especially in
21 situations where T cell help is lacking and expect to get
22 both the antibody and cytotoxic T cell responses.

23 Peptide *Brucella abortus* can generate mucosal
24 anti-HIV 1 antibody responses, and this approach may

1 protect from sexual and maternal fetal transmission of HIV
2 1.

3 Brucella abortus can be used as a carrier or
4 adjuvant in other situations where a Th1-like response is
5 desirable. What I showed you is also the components of the
6 Brucella, namely, the LPS, can be used to replace the
7 Brucella abortus and is effective as an immunogen in
8 inducing responses against small peptides.

9 Future directions of this research are to
10 optimize systemic and mucosal anti-HIV responses in monkeys
11 and then perform challenge experiments in monkeys using a
12 chimeric SHIV virus. So, the SHIV virus, or SHIV virus, is
13 the simian immune virus which has the AIDS envelope virus
14 and that's why it's called the SHIV virus. This can be
15 used to infect monkeys, but we can use constructs which
16 express the HIV 1 that infects humans to immunize these
17 monkeys and expect to get an immune response against the
18 envelope and then see if we can get protection against
19 challenge with these types of viruses.

20 We also plan to separate IgG subclasses and
21 assist the efficacy in neutralizing HIV 1 and to determine
22 whether Brucella abortus can serve as a carrier in other
23 situations where CD4 T cell help is limiting such as
24 protection against CMV in transplant recipients.

1 Mission relatedness of this research. HIV 1
2 research is a cross-cutting issue at CBER. It's a major
3 public health issue. As I showed you, recognition of the
4 importance of HIV research is that these granting agencies
5 provide support for laboratories performing this research
6 and we have been successful in getting this kind of support
7 from the Office of Women's Health and from the NIH
8 intramural targeted AIDS research group.

9 In terms of Office of Blood regulatory issues,
10 shortly after joining the group, I was asked to be the
11 chair for a pediatric AIDS license application. I'm
12 currently reviewing studies where they use HIVIG for
13 maternal fetal transmission. I've been asked to consult on
14 ELISA kits that have been used to detect HIV, and I've
15 asked to consult and advise groups that are setting up
16 ELISA kits for measuring antibodies against different viral
17 antigens.

18 In terms of mission relatedness, this is a
19 proactive idea that single isotypes rather than mixed
20 isotype IgIV therapy might be an issue of the future. We
21 have data that IgG2a in the mouse and there's data in the
22 literature that IgG3 in the human have greater antiviral
23 activity. So, we could understand a situation where
24 animals or humans would be immunized against a particular

1 antigen, and the actual isotypes would be purified and
2 these might be much more effective than the mixed
3 immunoglobulin therapy.

4 Antibodies against pro-inflammatory cytokines
5 should probably have no complement activating activity.
6 What I'm referring to here as an example that the
7 antibodies are being developed against factors such as TNF
8 for the treatment of sepsis. This is a condition
9 associated with large numbers of inflammatory cytokines
10 such as TNF. So, you wouldn't want to use antibodies to
11 block those cytokines that themselves have inflammatory
12 activity and you would want to use antibodies with no
13 complement activating activity.

14 What I'm getting at is that the type of
15 approach we have used to use carriers and adjuvants to get
16 a certain type of isotype response, similar approaches can
17 be used to get isotypes that have no complement activating
18 activity or to purify those antibodies. These might be
19 better ways of treating this type of condition.

20 The second project in the Laboratory of Plasma
21 Derivatives that I'm going to describe is a project that we
22 did to investigate cytokine release as a mechanism of
23 adverse effect induction following IgIV treatment.

24 IgIV preparations induced human monocytes to

1 secrete TNF-alpha, IL-1 beta, and IL-6 in vitro. These
2 cytokines are known to cause fever, chills, and headache,
3 symptoms commonly occurring in patients receiving IgIV.
4 Passage of these preparations over a polymyxin column which
5 removes LPS, removes the ability of the IgIV to elicit
6 these monokines. Anti-CD14 antibody, which binds the LPS
7 receptor on monocytes, blocked the effect of IgIV on
8 monocytes.

9 So, IgIV preparations induce inflammatory
10 monokines from being released. These monokines are
11 associated with the common adverse effects associated with
12 IgIV treatment. LPS in these preparations are probably
13 responsible for this effect since it can be avoided if LPS
14 is removed or if LPS receptors are blocked.

15 So, we think that if IgIV preparations are
16 treated in a way to remove more LPS, there would be more
17 limited adverse effects as a result of administration of
18 these products.

19 Future directions. We can use this approach to
20 look at other products and their excipients and test them
21 for ability to elicit inflammatory cytokines.

22 The mission relatedness of this research of
23 cytokines is a cross-cutting issue across CBER.

24 Adverse effects that you get from IgIV.

1 Similar adverse effects are also induced by OKT3 which is a
2 T cell antibody used in transplant medicine and can induce
3 a large number of cytokines.

4 These issues are cross-cutting in CBER and any
5 new product, whether it be recombinant or gene therapy or
6 other new product, can potentially stimulate cytokine
7 release. I think that it is important in CBER that we have
8 laboratories that can measure these cytokines and measure
9 the effect of these products or the excipients in vitro to
10 see what kinds of cytokines they release and use this
11 knowledge to make the product safer.

12 The next investigator that I'm going to talk
13 about is Dorothy Scott. She works in my lab. She's a
14 senior staff fellow. Her project is independently run by
15 her. She set it up independently. The title of the
16 project is Inhibition of Primary and Recall Allergen-
17 Specific Th2-Mediated Responses by a Th1 Stimulus, Isotype
18 Shift from IgE to IgG2a.

19 Her objectives were to determine whether a
20 strong Th1-like cytokine stimulus would inhibit primary and
21 recall IgE responses to an allergen, to determine whether
22 an ongoing allergic response could be abrogated by a strong
23 Th1-like stimulus, and to correlate the cytokine and
24 antibody isotype responses.

1 When *Brucella abortus*, a potent Th1-like
2 stimulus, was given together with the allergen, both
3 primary and recall IgE responses were inhibited. BA
4 administration was associated with increased IL-12 and
5 interferon-gamma but decreased IL-4 secreting cells. Anti-
6 IL-12 treatment abrogated the increase in interferon-gamma,
7 but did not reverse the effect of *Brucella abortus* on IgE,
8 suggesting that *Brucella abortus* induced an additional
9 factor or factors which inhibit the IgE.

10 An ongoing allergic response was also decreased
11 following *Brucella abortus* injection, and this was
12 associated with an increase in interferon-gamma secreting
13 cells.

14 In conclusion, a strong Th1-like stimulus can
15 abort allergic responses and decrease ongoing allergic
16 responses. This effect correlates with the induction of
17 Th1-like cytokines, for example, IL-12 and interferon-
18 gamma, and an inhibition of Th2-like cytokines, for
19 example, IL-4. So, IL-4 is the major cytokine involved in
20 switching from IgM to IgE.

21 Anti-IL-12 antibody treatment did not reverse
22 the effects of *Brucella abortus* completely, suggesting that
23 additional factors may be responsible for the inhibition of
24 IgE.

1 Future directions. I should say her results
2 indicate that an interferon-gamma independent pathway can
3 inhibit IgE responses, and this will be investigated by
4 looking for other factors that could be involved using
5 interferon-gamma knock-out mice. *Brucella abortus* has many
6 potent effects on the immune system. We will perform
7 studies of different components of the bacterium to
8 identify those that mediate desirable biologic effects.

9 Since induction of IL-12 is beneficial in
10 leishmaniasis, a parasitic disease, Dr. Scott is now
11 collaborating with people in parasitic diseases to test
12 whether *Brucella abortus* could enhance protection afforded
13 by a leishmanial vaccine.

14 Mission relatedness. A rare but life-
15 threatening adverse event following IgIV treatment is
16 anaphylaxis, particularly in patients with selective IgA
17 deficiencies. This is rare, but to show you something
18 recent related to this, last week there was a recall
19 situation because of one of the IgIV products was
20 associated with a relatively high incidence of allergic
21 effects following administration. We're now getting some
22 of this product and going to investigate it to try to
23 understand why this particular product was inducing what
24 looked like IgE-type immediate hypersensitivity reactions.

1 In replacement therapy for a genetic
2 deficiency, this can result in an immune response. So,
3 this is an individual who does not express this protein
4 from birth, and as a result, it's recognized as a foreign
5 antigen. An example is factor VIII treatment of
6 hemophilia. There's also obviously factor IX treatment.
7 These factors are associated with the inhibitors and can be
8 associated with true allergic reactions and is another
9 product at CBER that can induce an allergic response, and
10 it would be nice to know how to manipulate cytokines so as
11 to abort these responses. So, manipulation of the cytokine
12 milieu may abrogate these responses or at least modify them
13 so that a non-allergic response is elicited.

14 This is looking at Dr. Scott's research and my
15 research. So, this is the project in my lab, HIV 1
16 Immunotherapy Bypassing T Helper Cells. This is a project
17 in Dr. Scott's lab.

18 The one point I'd like to make is that these
19 projects are quite independent, and even though Dr. Scott
20 is using *Brucella abortus* and I'm using *Brucella abortus*,
21 she was actually doing research on *Brucella abortus* before
22 she came to my lab. It was one of the reasons why she
23 joined the lab. But we do share an interest in how
24 cytokines correlate with antibody responses, and obviously

1 we interact at that level.

2 I'd also like to point out that the approach
3 used for these projects can be thought of as a general
4 approach to induce immunity. In other words, if you know
5 what kinds of isotypes you want to obtain, you need to know
6 what kind of cytokines to use in order to induce these
7 isotypes, and having the right isotypes, you would then
8 have protection from a particular disease. An example I
9 gave was in the mouse, IgG2a against viral diseases.

10 Now, can say, well, this type of research is
11 related to making antibodies and it's very similar to what
12 is done in the Office of Vaccines. Why are we doing
13 research to get immune responses? Well, what we are
14 regulating is IgIV which is passive immunization. In order
15 to get to passive immunization, you need to generate those
16 antibodies.

17 What we are devising is a methodology to get
18 particular types of antibodies which are desirable in a
19 certain infectious disease scenario and which can be
20 purified and then used to treat that infectious disease
21 situation. So, this is an approach which could be used to
22 develop antibodies which could be developed in animals or
23 in man and then purified and used to treat in passive
24 immunization.

1 To just try and relate these projects to the
2 four of the six priority items that were referred to by Dr.
3 Finlayson as being priorities for research in the Office of
4 Blood, this project relates to the efficacy of immune
5 globulin preparations because it looks at different
6 isotypes and how these isotypes can be important in a
7 certain infectious disease. This project also is proactive
8 in the sense we are looking at treatments or methodologies
9 that could raise antibodies, new methods to make new
10 products for treating infectious diseases.

11 HIV, I think you would agree with me, is a
12 major public health issue and is a cross-cutting activity
13 related to other CBER programs.

14 In terms of Dr. Scott's project, clearly the
15 ability to manipulate cytokines so that you can suppress
16 allergic responses is a safety issue and is also a cross-
17 cutting issue across CBER and would relate to any product
18 that has the potential for inducing an allergic type or IgE
19 response.

20 Her research also relates to address unexpected
21 product events at a scientific level. As new products
22 become available, it is possible that they or their
23 excipients will induce allergic reactions.

24 Now we're going to Dr. Yu's research. These

1 are the two major projects in her lab. The first project
2 and the related project, Detection Characterization of HCV
3 RNA in Plasma-Derived Products and Correlation Between HCV
4 Screening of Donors and Lack of Antibodies Against HCV
5 Envelope Proteins in Ig Preparations. So, this refers to
6 IgIV and to the intramuscular form.

7 The results from her research. She has shown
8 that HCV transmission was associated with HCV present in
9 IgIV as determined by polymerase chain reactions which were
10 developed in her lab and are now used for lot release. The
11 implicated IgIV was derived from donors that were screened
12 for anti-HCV antibodies. So, the screening that I'm
13 referring to here is the second generation EIA 2 screen
14 that was approved to screen donors.

15 What she showed is that the IgIV made from
16 these donations was IgIV that was contaminated with HCV.
17 She showed in the laboratory that 15-fold more HCV was
18 removed during fractionation in the presence of anti-HCV
19 antibody compared to that in the absence of antibody. So,
20 by removing this antibody, you reduce the efficiency of the
21 removal of HCV that was present in the plasma pools.

22 She also went on to show that IgIV from
23 screened donors lacked activity against HCV envelope
24 proteins. In order to do this, she actually got

1 constructs, expressed the recombinant HCV envelope protein,
2 set up ELISA assays to measure those antibodies, and showed
3 that the IgIV from these donors lacked the antibodies that
4 bind to the envelope proteins, and those antibodies are
5 probably antibodies that are required for neutralization of
6 the antibody.

7 I'm just going to mention here that recipients
8 of immunoglobulin that develop HCV infections were
9 investigated by comparing sequences taking plasma from
10 these individuals, taking the implicated immunoglobulin and
11 amplifying PCR and then doing DNA sequencing. This is an
12 ongoing investigation to determine whether recipients of
13 this immunoglobulin really develop the HCV as a result of
14 this treatment. This will be the first description of
15 transmission of HCV by immunoglobulin, the intramuscular
16 product. So, we do not have proof of this, but this is an
17 ongoing investigation at this time, and I explained to you
18 how that is going on.

19 In her future studies, Dr. Yu will identify the
20 nature of antibodies which form complexes with and
21 neutralize HCV. She will study glycosylation and
22 immunoreactivity of expressed E1 and E2 envelope proteins,
23 and she will also search for HCV receptors in hepatocytes
24 or cell lines.

1 The mission relatedness is very clear.
2 Transmission of HCV represents a serious threat to plasma-
3 derived products. Research directed towards an
4 understanding of the mechanisms involved in transmission
5 will help prevent future cases. Developing sensitive PCR
6 method for lot release provides assurance that products
7 will be safe.

8 Now I'm going on to Dr. Shrake's research. I'm
9 going to have to go through this more quickly. The first
10 project that I'm going to describe is Ramifications of the
11 Linkage Between Ligand Binding and Protein Denaturation and
12 Intra- and Inter-Protein Interactions with Respect to
13 Protein Stability and Structure.

14 I'm going to go through these conclusions.
15 What he has shown is that biphasic denaturation in the
16 presence of a ligand -- what we're talking about are
17 saturated fatty acids -- does not relate to unfolding
18 different parts of the same molecule, but rather to
19 unfolding different kinds of molecules, those with low
20 levels of bound ligand and those with higher levels.
21 Distinguishing between these two mechanisms is crucial when
22 interpreting protein unfolding data. This mechanism has
23 been modeled thermodynamically.

24 He has shown that coupling between the

1 unfolding equilibrium and the disulfide-mediated
2 dimerization of partially and fully unfolded albumin
3 monomers is responsible for the two unfolding events in
4 unblocked protein. Blocking the free sulfhydryl precludes
5 such dimerization and yields a single unfolding transition.

6 He's also shown that the binding of halide
7 anion promotes a conformational change in the protein
8 resulting in a form that undergoes essentially ideal two-
9 state unfolding.

10 Future directions. Immediate goals are
11 identifications of the regions of human albumin involved in
12 the two major heat-induced unfolding transitions at low
13 ionic strength and neutral pH, location of the principal
14 halide anion binding site and thermodynamic modeling of the
15 two extreme protein forms, that which undergoes non-
16 cooperative unfolding and that which undergoes concerted,
17 highly cooperative unfolding. In the longer term, the
18 causes and ways of minimizing the polymerization of
19 proteins during folding or refolding will be studied as
20 well as polymerization of native proteins.

21 Mission relatedness. Results from these
22 studies on the thermal stability of human albumin, as well
23 as other studies, have facilitated the licensing of the
24 first albumin product with a single stabilizer, that is,

1 using caprylate only.

2 The destabilization of commercial albumin by
3 organic solvent treatment during processing is now
4 understood in terms of the removal of bound endogenous
5 fatty acids which stabilize the protein.

6 Understanding fundamental aspects of thermal
7 stabilization of proteins is relevant in general since a
8 variety of licensed biologic products undergo heating as a
9 viral inactivation procedure.

10 The second project of Dr. Shrake's relates to
11 the characterization of non-protein colloidal plasma volume
12 expanders. I'll just go through the conclusion.

13 Comparison of HPLC methods from eight
14 manufacturers showed that only the method of a single
15 manufacturer gives accurate weight and number average
16 molecular weight values for hetastarch, and this is the
17 basis for using this method to measure hetastarch potency.

18 Experience determining number average molecular
19 weights from osmotic pressure data from Dextran 70 and
20 Dextran 40 has permitted participation in setting molecular
21 weight specifications for these products in the proposed
22 USP monograph. As a result of this collaboration with the
23 USP, a set of universal virial coefficients was derived
24 that permit the accurate calculation of the oncotic

1 pressure for Dextran over broad ranges of molecular weights
2 and concentrations.

3 Comparing two approaches to calibrate size
4 exclusion HPLC for Dextran molecular weight determinations,
5 to establish which is preferable for the USP monograph.
6 So, what I'm talking about here are these future
7 directions. He wishes to attempt to obtain clinical data
8 from the literature which will permit the estimation of
9 vascular bed permeability to Dextran from a resuscitation
10 model and to develop a generally available set of
11 hetastarch molecular weight standards for HPLC molecular
12 weight.

13 The mission relatedness of his research. He
14 has validated the size exclusion HPLC as a methodology
15 which allows approval of the first generic hetastarch
16 product. The existence of approved USP monographs with
17 Dextran 70 and 40, as well as hetastarch, provide a great
18 deal of regulatory relief to the agency since the
19 monographs define the direct substances and products
20 avoiding issues of sameness when considering potential
21 generic products.

22 I'm getting close to the end. I know this has
23 been a very long presentation, but I'm trying to give full
24 justification to the people who have done all this work.

1 The investigator for this project is Suong Tran
2 who is in the laboratory of Andrew Shrake. The title of
3 her project is the Folding Pathways for Alpha-1 Proteinase
4 Inhibitor.

5 The rationale for the project. Alpha-1
6 proteinase inhibitor is a serine proteinase inhibitor, a
7 serpin that acts on elastase and limits tissue destruction.
8 Serpins have a tendency to polymerize which renders them
9 inactive. She wished to study folding conditions that
10 maintain the stability and function of the monomer and
11 avoid polymerization.

12 Her results showed that polymerized protein
13 unfolds at higher temperatures and higher denaturant
14 concentration than the monomer. The folding rate of the
15 polymer is tenfold slower than that of the monomer.

16 In the presence of low concentrations of the
17 denaturant quantity, the monomer unfolds to an intermediate
18 state as shown by HPLC. Polymerization occurs as partly
19 unfolded monomers interact.

20 Conclusions. The polymerized protein is more
21 stable than the active monomer. The folding of alpha-1-PI
22 involves intermediate species. Polymerization can be
23 minimized by controlling the conditions for the
24 intermediates, e.g., temperature and presence of

1 denaturants.

2 Mission relatedness. Alpha-1-PI is a licensed
3 product regulated by the Laboratory of Plasma Derivatives.
4 The studies of the folding of this protein relate to its
5 manufacture, efficacy, and stability. The results of these
6 experiments can be used to design modified molecules with
7 enhanced activity and/or stability.

8 So, how do we work as a group? What this slide
9 is trying to depict is how the various sections, the Viral
10 Safety Section, the Immunology Section, and the Protein
11 Chemistry Section, interact as a group. What I hope I've
12 clearly shown you in the first part of my presentation is
13 that these groups and expertises are required to regulate
14 the products that we're looking at. So, without a viral
15 safety expert, a protein chemist, and immunologist, I think
16 it would be very difficult to regulate these products.

17 But how do we interact at a research level? We
18 have a weekly meeting where we discuss work in progress.
19 What I've tried to indicate here is that it's very clear
20 that both Dr. Yu's group and my group are interested in
21 viral pathogenesis and protection, which is an area of
22 interaction between our two groups. What I've listed as an
23 area of interaction between the three groups is protein-
24 ligand interaction. Clearly to look at envelope proteins

1 and how they interact with antibodies relates to protein-
2 protein interactions.

3 In my group identifying peptides and
4 identifying the methodology, the chemistry involved in
5 linking the peptides to carriers involves chemistry. In
6 general in immunology, interaction of antigen and
7 antibodies and ligands and the receptors involves protein-
8 protein interactions.

9 Protein-ligand interactions are obviously the
10 major theme in Dr. Shrake's lab and this ties our three
11 groups together.

12 What I would say is that even though we come
13 from diverse backgrounds, we're able to meet on a regular
14 basis both formally and informally to discuss our projects
15 in a meaningful way and learn from each other which helps
16 our research and which helps us perform our regulatory
17 duties.

18 Thank you.

19 DR. SWISHER: Thank you, Dr. Golding.

20 Are there questions from the committee? Yes.

21 REV. LITTLE: Dr. Golding, I have a question
22 about the project on the cytokine release. I've had three
23 separate instances of what was labeled chemical meningitis
24 following infusions of IVIG. I was wondering if this is

1 part of the inflammatory process that you're referring to.

2 Also, are there products now that exist that
3 have this removal of the -- is it LPS? Is that what you
4 said?

5 DR. GOLDING: Well, in terms of aseptic
6 meningitis, aseptic meningitis is a known complication of
7 IgIV therapy. It's now asked of manufacturers that they
8 state in their label that aseptic meningitis is a possible
9 side effect after using IgIV.

10 What the cytokine basis for that is, as far as
11 I know, is unknown, but I think what you've pointed to is
12 an area which should be looked at. What I would think as a
13 possibility that certain cytokines are released at the
14 blood brain barrier when you infuse IgIV and that those
15 cytokines are responsible for the meningitis.

16 I would think that the type of cytokines that
17 we have looked at like TNF and IL-1 are candidates that I
18 would put high on the list as being possible mediators of
19 this reaction. So, I think you put your finger on a
20 situation which is very worthwhile to look at and shows the
21 connection between cytokines and these products that we're
22 looking at.

23 Your second question relating to LPS. We are
24 going through a process now of looking at different

1 fractionators and looking at the bioburdens. One of the
2 things that stands out is that because of the nature of the
3 process, there often is a high bioburden in these products
4 and the manufacturers obviously do a sterile filtration to
5 remove bacteria, but the sterile filtration does not remove
6 lipopolysaccharide. It is a problem in the industry that
7 they often end up with high amounts of LPS or endotoxin in
8 the final product. The release test is a rabbit pyrogen
9 test which has been used for many years.

10 But it is also possible to measure LPS in these
11 preparations even though that's not the release test. We
12 often find that the LPS levels are measurable and are
13 detectable and on a level which we know can induce the type
14 of reaction that we're seeing in the laboratory.

15 So, that research and the finding out there in
16 industry tells me that what we should try and do is find a
17 way of removing more LPS from the product and I think we
18 would get rid of these -- 10 percent of infusions are
19 associated with chills and fever and headache. If you give
20 the infusions more rapidly, you probably approach 80
21 percent or 100 percent of the patients getting it. I'm
22 convinced that one of the factors is the
23 lipopolysaccharide.

24 DR. HOLMBERG: You explained to us about your

1 overlapping of different laboratories and meeting on a
2 weekly basis, but where's the intersection of all of this?
3 Are you collaborating together on any focused research?

4 DR. GOLDING: Well, several of the projects
5 lead to interactions and discussions and sharing of
6 technical expertise. I'll give you one example.

7 In my laboratory -- and this is supervised
8 mainly by Dr. Scott -- she set up very sensitive techniques
9 to measure cytokines using PCR. In Dr. Yu's laboratory,
10 PCR is used mainly to look for viral contamination of
11 products. It's clear that many of these IgIV or Ig
12 preparations which we're looking at mainly today, if they
13 are contaminated, have very low levels of contamination.
14 It's very important to modify the PCR so that it will be
15 highly sensitive and also consistent.

16 There's a lot of discussion between the
17 different people in the different groups. We meet on a
18 weekly basis and this is the type of thing that we'll
19 discuss.

20 Another issue that has come up. We haven't
21 developed a research project for it, but it has come up and
22 we're starting to think about it very seriously. It's
23 something for the future. I'm sure you're aware of prions
24 and CJD. This is a very cross-cutting issue, very

1 important in blood products, and is very important in our
2 laboratory.

3 So, we have a protein chemist. We have an
4 immunologist and we have virologists and we have started a
5 discussion group to talk about possible projects that we
6 can do which will be unique to look at prions and possible
7 contamination of blood-derived products with prions.

8 So, those are just some examples, but in
9 general, if I have a protein problem, the first place I'll
10 go to is Andy Shrake or Suong Tran, and if there are
11 problems related to my work which relate to virology, I'll
12 go and speak to Mei-ying and her group. So, besides
13 meeting on a regular basis, there are many informal
14 meetings.

15 We don't have a particular project at the
16 moment which is really a project where members from the
17 separate groups are actually contributing, but the prion
18 area is one area that we're looking at very seriously to
19 try to develop a project where members of each group will
20 be involved.

21 DR. SWISHER: Dr. Nelson.

22 DR. NELSON: I had a question. You mentioned
23 that Dr. Yu had had some data on the intramuscular
24 immunoglobulin and hepatitis C and she was sequencing the

1 viruses from the product and from some of the people that
2 were infected. Does the data suggest that the
3 intramuscular immunoglobulin transmitted hepatitis C, or is
4 it too early to make that conclusion?

5 DR. GOLDING: Well, there isn't a definite
6 conclusion. There was a single patient who was infected
7 with HCV. He was a traveler. He received Ig. There was
8 no obvious risk factors except as a child he was involved
9 in an accident and may have had some transfusion.

10 His plasma and the implicated Ig lot were
11 obtained by Dr. Yu's laboratory and what they did is they
12 amplified different regions of the HCV genome using
13 different PCR primers and then, working with Dr.
14 Feinstone's laboratory, sequenced those regions.

15 The results were not clear in the sense that
16 there was high homology between the plasma -- one region of
17 the plasma HCV and the Ig from the lots were highly
18 homologous and were different from other HCV isolates that
19 you would find in the U.S. But there was another region
20 that was different between the plasma and the patient,
21 sufficiently different to think that they really did come
22 from two sources.

23 So, as a result of all that analysis, we cannot
24 be sure that that patient actually received that Ig lot.

1 There's like conflicting data.

2 What has been done as an ongoing study with the
3 CDC -- and the CDC are playing the primary role here --
4 they have gone to the clinic where their patient received
5 that Ig lot, have identified over 100 individuals, taken
6 blood from them, and tested them. All those individuals
7 were negative. The normal incidence is somewhere around 5
8 percent. So, even if one or two were positive, that
9 wouldn't have been helpful. So, as far as we can tell,
10 this Ig lot did not transmit the disease.

11 But that work we think was very important and
12 the methodologies involved that she has developed in her
13 lab are very critical in trying to investigate this which
14 has very far-reaching implications in terms of Ig treatment
15 of travelers.

16 DR. SWISHER: Other questions?

17 DR. HOLMBERG: I think this is very responsive
18 for Dr. Yu to respond to the mapping of the nucleic acid.
19 However, who sets the priority for the research?

20 DR. GOLDING: Well, I think what you are asking
21 is a difficult question. I think it's evolving now at CBER
22 at the highest levels and at the division levels. What is
23 happening is it's evolving into a situation where we're
24 being told more and more what the priorities of the

1 research are, and I think we're going to be told which
2 particular projects should be pursued and which shouldn't
3 be pursued. But this is a new development at CBER.

4 Until a few years ago, each investigator was
5 doing investigator-initiated research. He was presenting
6 his research in different meetings, at seminars, site
7 visits and so on, and he was getting feedback from the
8 people around him, including his supervisors, and if there
9 was a problem with his research, he would know about it.
10 One of the measures of his research was his productivity,
11 and we also have a Promotion and Review Committee which
12 would look at that research in terms of its productivity.

13 The whole idea of the research being strictly
14 mission related is a relatively new idea. I don't know how
15 many BPACs you've been to where you've heard site visits.
16 I don't know if you've heard a presentation before where
17 we've actually tried to relate our work to the mission of
18 CBER. So, as far as I know, this is a relatively new
19 development and it's going to increasingly become an issue
20 at CBER that we will need to justify our research in terms
21 of our mission.

22 What's going to happen besides this type of
23 presentation is that there is going to be a CBER oversight
24 committee that is going to look at all the research

1 programs and decide which research programs should be
2 supported and which shouldn't be supported.

3 DR. SWISHER: Other questions?

4 (No response.)

5 DR. SWISHER: Thank you very much, Dr. Golding.

6 I think we are ready now for our closed
7 session. Those of our guests and observers will please
8 clear the room as quickly as possible and the CBER staff
9 people.

10 (Whereupon, at 10:15 a.m., the committee
11 recessed, to reconvene in closed session.)

12

13