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FOOD AND DRUG ADMINISTRATION

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CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

BIOLOGICAL RESPONSE MODIFIERS ADVISORY COMMITTEE

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OPEN SESSION

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THURSDAY,
APRIL 5, 2001

The Committee met in the Second Floor Ballroom at 8120 Wisconsin Avenue, Bethesda, Maryland, at 9:00 a.m., Daniel Salomon, M.D., Chair, presiding.

Present:

DANIEL R. SALOMON, M.D., Chair
RICHARD E. CHAMPLIN, M.D., Member
RICHARD C. MULLIGAN, Ph.D., Member
EDWARD A. SAUSVILLE, M.D., Ph.D., Member
ABBEY MEYERS, Consultant
W. MICHAEL O'FALLON, Ph.D., Consultant
ALISON F. LAWTON, Non-Voting Guest
GAIL DAPOLITO, Executive Secretary
ROSANNA L. HARVEY, Committee Management Specialist

Also Present:

STEPHEN J. CHANOCK, M.D.
AMY PATTERSON, M.D.
BLAKE J. ROESSLER, M.D.
STEVEN R. BAUER, Ph.D.
THOMAS L. EGGERMAN, M.D., Ph.D.
SUZANNE EPSTEIN, Ph.D.
JOYCE L. FREY-VASCONCELLS, Ph.D.
PATRICIA KEEGAN, M.D.
MARY ANNE MALARKEY
PHILIP D. NOGUCHI, M.D.
JOSEPH P. SALEWSKI
MARJORIE A. SHAPIRO, Ph.D.

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Also Present (cont.)

JAY P. SIEGEL, M.D.
KAREN D. WEISS, M.D.
CAROLYN A. WILSON, Ph.D.
SALLY SEAVER
JANET ROSE CHRISTENSEN
NEIL GOLDMAN
WILLIAM FREAS
KATHRYN C. ZOON, Ph.D.

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

2 9:10 a.m.

3 DR. SALOMON: Good morning, everyone. I'd
4 like to get everyone to sit down now and initiate this
5 meeting today, April 5, 2001, Biological Response
6 Modifiers Advisory Committee.
7 I decided coming here that one of the
8 things that we need to do from here on in is title
9 these meetings because I never really quite know what
10 to say after this. You know, this is the 18th Annual
11 -- we'll have to work on that one.
12 Okay, anyway, welcome everyone. I know
13 it's always something to make time in busy schedules
14 to participate in these meetings and I say that both
15 for our expert panel as well as visitors and the
16 representatives of several government agencies that
17 are here and I hope everyone will feel welcome and
18 also feel like they had an opportunity to participate
19 actively in the deliberations of the committee over
20 the next two days.
21 Certainly, if anyone on any part of the
22 table or in the audience feels they're not getting a
23 chance, that they should definitely feel comfortable
24 to come and talk to me at the break because that would
25 not be my strategy.

1 I'd like to turn to Gail Dapolito to read
2 into the orders the Conflict of Interest Statement.
3 MS. DAPOLITO: Thank you, Dr. Solomon.
4 This announcement is made part of the public record of
5 the April 5-6, 2001 meeting of the Biological Response
6 Modifiers Advisory Committee pursuant to the authority
7 granted under the Committee charter, the Director of
8 FDA Center for Biologics Evaluation and Research has
9 appointed Ms. Abbey Meyers and Dr. Michael O'Fallon as
10 temporary voting members. To determine if any
11 conflicts of interested existed, the Agency reviewed
12 the submitted agenda and all financial interests
13 reported by the meeting participants. As a result of
14 this review, the following disclosures are being made:
15 in accordance with 18 U.S.C. 208, Dr. Richard Mulligan
16 has been granted a waiver which permits him to
17 participate in the Committee discussions. Drs.
18 Champlin, Kurtzberg, Salomon and Sausville and Ms.
19 Meyers have associations with firms that could be
20 affected by the Committee discussions. However, in
21 accordance with current statutes, it has been
22 determined that none of these associations require the
23 need for a waiver, a written appearance determination
24 or an exclusion.
25 In regards to FDA's invited guests, the

1 Agency has determined that the services of these
2 guests are essential. The following interests are
3 being made public to allow meeting participants to
4 objectively evaluate any presentations and/or comments
5 made by the guests: Dr. Steven Chanock is employed by
6 the National Cancer Institute, National Institutes of
7 Health; Ms. Alison Lawton will be serving as a
8 non-voting industry representative for this meeting.
9 She is employed by Genzyme. Genzyme has associations
10 with various universities, investigators and research
11 foundations that are involved in gene therapy. Ms.
12 Lawton also has interests in several firms that could
13 be affected by the Committee discussions. Dr. Amy
14 Patterson is employed by the National Institutes of
15 Health, Office of Biotechnology Activities. Dr. Blake
16 Roessler is employed by the University of Michigan and
17 has interests in the field of plasmid vector
18 production that could be affected by the Committee
19 discussions.
20 In the event that the discussions involved
21 other products or firms not already on the agenda for
22 which FDA's participants have a financial interest,
23 the participants are aware of the need to exclude
24 themselves from such involvement and their exclusion
25 will be noted for the public record.

1 With respect to all other meeting
2 participants, we ask in the interest of fairness that
3 you state your name, affiliation and address any
4 current or previous financial involvement with any
5 firm whose product you wish to comment upon. A copy
6 of the waiver addressed in this announcement is
7 available by written request under the Freedom of
8 Information Act.
9 And just a household item, housekeeping
10 item, we would like to request, just as a courtesy
11 during the Committee deliberations that you turn your
12 cell phones and pagers off or put them on the silent
13 mode and if you wish to speak on your cell phone
14 please go into the foyer.
15 Thank you.
16 DR. SALOMON: Thank you, Gail. Another
17 little quick thing from the Chairman's perspective,
18 just housekeeping is if you notice the red light, red
19 light off, I think most everybody here has been on
20 this Committee before, so this is not news, but just
21 remember to turn it on and off during your -- after
22 you've made your comments because otherwise you get
23 feedback through the loop and they won't be able to
24 get the kind of recording that's necessary to keep
25 track of all of this.

1 Usually, what we've done at the very
2 beginning is just gone around the table really
3 briefly, again, not so much for our sake, but for the
4 visitors' sake, to know who's sitting on the Panel.
5 If you can just give a sentence, a name and a sentence
6 or two about why you're here, what your area of
7 expertise is.
8 Amy, do you want to start?
9 DR. PATTERSON: Yes. I'm Amy Patterson.
10 I'm Director of the Office of Biotechnology Activities
11 in the Office of the Director of NIH. My office
12 houses three federal advisory committees, one on
13 genetic testing, the Secretary's Advisory Committee on
14 Genetic Testing; one on xenotransplantation and the
15 third and probably most relevant to today is the NIH
16 Recombinant Advisory Committee.
17 DR. CHANOCK: Yes, I'm Stephen Chanock, an
18 Investigator in the Pediatric Oncology Branch and
19 particularly the Immunocompromised Host Section with
20 a strong interest in infectious disease and
21 immunocompromised hosts. I'm a consultant for
22 infectious disease at the Clinical Center and I also
23 serve on the Institution of Biosafety Committee for
24 the NIH.
25 MS. LAWTON: I'm Alison Lawton. I'm

1 Senior Vice President of Regulatory Affairs for
2 Genzyme Corporation. I'm the Industry Rep. I'm also
3 the Chair of Cell and Gene Therapy Committee for the
4 PhRMA Industry Association.
5 MS. MEYERS: I'm Abbey Meyers, President
6 of the National Organization for Rare Disorders known
7 as NORD. I'm a former member of the RAC and I'm
8 currently on the National Human Research Protection
9 Advisory Committee.
10 DR. MULLIGAN: I'm Rich Mulligan from
11 Harvard Medical School and I'm involved in gene
12 transfer research and stem cell research.
13 DR. CHAMPLIN: Richard Champlin. I'm from
14 the M.D. Anderson Cancer Center. I'm a hematologist
15 and Chairman of the Blood and Marrow Transplant
16 Department.
17 DR. O'FALLON: Michael O'Fallon from the
18 Mayo Clinic. I'm a biostatistician.
19 DR. SALOMON: Dan Salomon from the Scripps
20 Research Institute in LaJolla, California. My
21 interests are in organ and cell transplantation and
22 gene transfer.
23 MS. DAPOLITO: Gail Dapolito, CBER,
24 Committee Executive Secretary and the Committee
25 Management Specialist, Rosanna Harvey. Thank you.

1 DR. SAUSVILLE: I'm Edward Sausville. I'm
2 the Associate Director for NCI's Developmental
3 Therapeutics Program, involved in the discovery and
4 development of drugs and biologics for early clinical
5 trial and I'm a Medical Oncologist.
6 DR. WILSON: Carolyn Wilson, a member of
7 the Division of Cellular and Gene Therapies at CBER,
8 FDA.
9 DR. FREY-VASCONCELLS: Joyce Frey, Deputy
10 Director for Cellular and Gene Therapies.
11 DR. NOGUCHI: Phil Noguchi, Director of
12 Cell and Gene Therapy in the Office of Therapeutics at
13 CBER.
14 DR. SIEGEL: Jay Siegel, Director of the
15 Office of Therapeutics Research and Review at CBER.
16 DR. SALOMON: Okay, thank you all very
17 much. Unless there's anything that needs to get read
18 into the record at this point, I'd like to get
19 started.
20 Dr. Joyce Frey is going to present to us
21 an overview of the March 6, 2000 FDA Gene Therapy
22 Letter which then leads into a discussion on the
23 responses to the gene letter and some of its
24 implications in terms of discussion of the Committee.
25 DR. FREY-VASCONCELLS: Okay, today I'd

1 like to give you an overview of the famous March 6th
2 letter and kind of the process that we went through in
3 issuing this letter and reviewing the responses.
4 Next slide. There are several reasons
5 that we issued this letter. One of them was safety
6 concerns related to recent events. This included the
7 death of a patient on a gene transfer protocol and the
8 conduct of that trial. There was also a report of
9 potential risk of transmission of infectious agents by
10 inadequately tested product. And then finally, there
11 were violations that the Agency noted on several
12 directed inspections.
13 In addition, we realized that gene
14 transfer was a rapidly developing field and over ten
15 years a lot of things had changed. So standing
16 testing requirements that the Agency was looking when
17 the field began, began 10 years ago, is clearly not
18 adequate by today's standards.
19 In addition, based on our regulations for
20 annual reporting, for product information, a sponsor
21 is only required to submit a summary of significant
22 manufacturing or biological changes. So it's very
23 difficult for the Agency to ensure over time whether
24 sponsors were changing and testing their product by
25 current standards. Generally, what we would receive

1 in annual reports is no deviations on sterility.
2 Well, I think you can all see where that's probably
3 not sufficient information for a novel technology.
4 Next slide. So we went through the
5 process of getting experts, both from product and
6 clinical and pre-clinical together, and trying to
7 figure out what information does the Agency need to
8 receive in order to address our concerns that were
9 listed in the previous slide. Once we had identified
10 what issues, what information we wanted to received,
11 we issued the famous March 6th letter. In that
12 letter, because of what had happened with the death of
13 a patient and report of potential transmission of an
14 infectious disease, we actually put a 3 month time
15 line for sponsors to respond to this letter. We
16 realized that this was an enormous task, both for the
17 Agency and for sponsors, but in talking to industry
18 and people that were in this field, everyone felt that
19 this was an effort that clearly needed to happen and
20 needed to happen in a relatively short period of time.
21 So about March 7th we had received basically all of
22 the responses from all the active files. In those
23 responses, we reviewed them and we analyzed the data
24 for each vector system and as you can see by the
25 agenda, we're going to be discussing specific issues

1 related to three different vector systems.

2 We also wanted to identify whether there

3 were common problems in regulatory compliance across

4 the board that would be to all areas and I'm actually

5 going to be talking about two of those at the end of

6 my talk.

7 In addition, with this information it

8 helped us to identify areas where we needed to

9 increase our training and outreach. Based on the

10 information, we have proposed draft policy

11 recommendations that will be discussed and finally to

12 seek outside advice on these recommendations and

13 that's part of the purpose of today's meeting.

14 Next slide. I'm going to focus mainly on

15 the product questions. There were seven questions in

16 the letter. I'm going to talk about the first five.

17 And then this afternoon, Question 6 which related to

18 the clinical trials and 7, the preclinical, will be

19 discussed by Drs. Karen Weiss and Pat Keegan.

20 For product questions what we wanted to

21 know was we wanted a list of all gene transfer

22 products, cell banks and viral banks that were ever

23 produced in your facility. What we had noticed over

24 the years was when gene transfer first started, most

25 people were making one product in their facility using

1 one cell bank or one viral bank. What had happened
2 over time is due to relationships with companies and
3 things like that, people were making multiple gene
4 transfer products and it was also a mechanism for us
5 to find out what areas did we need to start thinking
6 about in relation to facility-type information.
7 The second question was a list of cross
8 reference files. There was a lot of people that were
9 cross referencing and we weren't really sure that we
10 had a good handle on who was cross referencing who.
11 So we wanted a list of both what files you -- the
12 sponsor cross referenced and what files the sponsor
13 had authorized to cross reference their file.
14 Then Question 3 was probably the most
15 intensive. And that was a list of all lot release and
16 characterization data for each lot and each cell bank
17 and viral bank that had been produced to date.
18 The fourth question was reasons for
19 rejecting lots. This was so that we could get a feel
20 for were there particular areas, vectors systems that
21 we needed to keep a close eye on, were there common
22 reasons for rejecting lots, were there certain
23 facilities that were having problems that we needed to
24 work with?
25 The fifth question was the quality

1 assurance program. We wanted to ensure that there
2 were appropriate checks and balances in manufacturing
3 and releasing product in order to treat subjects.
4 And then finally, we asked sponsors to
5 commit to yearly updates of this information. That
6 doesn't mean that they have to submit all their lot
7 release and characterization data on all lots ever
8 produced each year. It was an update on that
9 information.
10 Next slide. The goals that we had set for
11 this letter was (1) to ensure that all gene transfer
12 products met today's testing standards. That was
13 really the most critical thing we wanted to get out of
14 this. The second one was to evaluate the testing
15 requirements. Were there areas that we needed to make
16 the testing requirements more stringent? Were there
17 areas that we had gained enough experience that we
18 could potentially relax the testing requirements?
19 Then we wanted to use this information to
20 provide appropriate guidance and also to be able to
21 look to areas on what we needed to focus in order to
22 move these products towards licensure. It was also a
23 mechanism by which we could increase public confidence
24 in our oversight ability and then it also provided a
25 mechanism for ensuring annual reporting of

1 information, adequate product information to the
2 Agency so that we could have proper oversight. And
3 then finally, to increase, to identify the training
4 and outreach needs and to develop appropriate policy
5 recommendations.

6 Next slide. Okay, there were two areas
7 that we had identified, that there was -- that the
8 Agency had not been real clear as to exactly what we
9 wanted to see. And one of them was the area of
10 potency. The CFR defines potency as a test shall
11 consist of either in vitro or in vivo tests, or both,
12 which have been specifically designed for each product
13 so as to indicate its potency and then potency is
14 actually defined as a specific ability or capacity of
15 the product to affect a given result.

16 Next slide. What we meant by potency is
17 actually a measure of biological effect. It's a
18 functional activity of your product. A lot of
19 sponsors we noted wanted to use a measurement of viral
20 titers, their potency. The problem with doing this is
21 that if something happens during your manufacturing
22 process and you lose your gene insert, just measuring
23 viral titer will not detect that you have lost your
24 gene insert.

25 Another common measurement that people

1 wanted to use for potency was gene expression and we
2 actually do allow gene expression for potency in their
3 early phase of product development. But as you move
4 towards licensure, you need to move to a more
5 functional assay. The problem with gene expression is
6 that protein may be expressed, but your gene may be
7 mutated slightly to where the protein that's expressed
8 is actually not active. If all you're measuring is
9 gene expression, you're not going to pick up that your
10 gene actually, that the protein is actually not
11 active.
12 Next slide. The next area that I'd like
13 to talk about that we have increased actually the
14 testing is the testing for adventitious viral testing
15 and that is what we're asking now is that on each
16 production lot you do an in vitro viral testing and
17 this is usually done either on the lysate or the end
18 of production cells.
19 Next slide. So this morning's session,
20 the first talk following mine will be more of a
21 training outreach on Question 5 and what constitutes
22 a quality assurance program. And then also to discuss
23 issues related to multi-use facilities. Then
24 following that there will be three different
25 discussions on policy recommendations that we're

1 seeking advice on. The first one will be on RCR and
2 the appropriateness of different packaging cell lines.
3 The second policy recommendation will be for testing
4 of plasmids when plasmids are used as intermediates to
5 produce the gene transfer product. And then the final
6 discussion will be on adenovirus vector titer
7 measurements and RCA levels.
8 So I think I'll turn the mike over to Ms.
9 Mary Malarkey to talk about quality assurance.
10 DR. SALOMON: Joyce, can I ask a question
11 or two, briefly?
12 DR. FREY-VASCONCELLS: Sure.
13 DR. SALOMON: So just so that I have the
14 right context for this, you looked at a minority of
15 the total programs in the country. You took a random
16 sampling.
17 DR. FREY-VASCONCELLS: You mean for the
18 inspection part?
19 DR. SALOMON: Uh-huh.
20 DR. FREY-VASCONCELLS: Right.
21 DR. SALOMON: And so can you -- if we're
22 going to get to this later, then you can tell me wait
23 for the next talk, but one key question I think is how
24 did you do a random -- how is this random? I mean if
25 we're trying to reassure everybody that this was done

1 right.

2 DR. FREY-VASCONCELLS: Oh good, I don't
3 have to answer this. No, there's actually going to be
4 a talk this afternoon by the compliance and discuss
5 how the randomization was done. So I think I'd rather
6 let -- since I was not involved directly.

7 DR. SIEGEL: Let me just put that into a
8 framework. The March 6th letter that's been discussed
9 was sent to every sponsor doing gene therapy and every
10 sponsor going gene therapy sent us a response
11 regarding their viral testing, their validation, their
12 test methods, their quality control for manufacturing
13 and the talks you're going to hear this morning are
14 based on those responses and interactions with the
15 sponsors. So that is 100 percent overview of what we
16 regulate.

17 Similarly, it's on the clinical practices,
18 clinical oversight and clinical monitoring. We got
19 responses from everybody to the same letter and in
20 terms of what they do, but we sent inspection teams
21 out to a random sampling. Those were good clinical
22 practices inspections. We did some good manufacturing
23 practices inspections, but those were not part of the
24 random process. Those were for cause where we had
25 specific concerns. So that will be discussed this

1 afternoon, but it's not terribly pertinent to this
2 morning's topics.
3 DR. SALOMON: Okay, thank you. I actually
4 didn't understand that as well as I should have.
5 The second question I had was is it
6 reasonable to ask what would be then -- this was sort
7 of the first fly at what kind of things was out there,
8 what kind of information you get back and then -- but
9 use some of that information to help guide the policy
10 decisions.
11 DR. FREY-VASCONCELLS: Right.
12 DR. SALOMON: What do you see, in general,
13 at this point, in terms of going forward in the
14 future? Would this be a yearly event? Would this be
15 a constant reporting requirement from these sort of
16 production facilities? Would it be individualized?
17 You need to show this, this and this before we'd allow
18 you to have an IND.
19 DR. FREY-VASCONCELLS: Well, what we ask
20 is first of all for anybody submitting a new IND, yes,
21 they have to answer all the questions in the March 6th
22 letter. In addition, so that we can maintain proper
23 oversight, we are asking people to update the
24 information requested in this March 6th letter on a
25 yearly basis. In the letter, there's language that we

1 -- for convenience, you can submit it in your annual
2 report, but we want to see this information on a
3 yearly basis. That way we can keep closer tabs on
4 each vector system and what people are seeing and
5 that's why we want updates on why people are rejecting
6 lots. And then that way -- right, we can develop
7 appropriate policy recommendations and have further
8 discussions as we see trends in vector productions.
9 DR. SALOMON: One more question, and
10 again, I personally think this is an extremely
11 important thing that we're talking about here today.
12 This, to me, is about as important as anything we've
13 had in front of the Committee for a long time in terms
14 of its implications about and its impact on the way
15 we'll be doing gene therapy in many different sites
16 around the country.
17 So one of the questions I have is right
18 now, correct me if I'm wrong, but right now, there is
19 no official certification for a gene therapy
20 production facility.
21 DR. FREY-VASCONCELLS: Right. I guess I'm
22 not quite sure how -- what you mean by quote
23 certification.
24 DR. SALOMON: Well, I mean for example,
25 clinical laboratory has to be CLIA certified.

1 DR. FREY-VASCONCELLS: Right.

2 DR. SALOMON: And all the technicians in
3 the laboratory have to have CLIA certification and
4 that's necessary for any data that is reported to a
5 physician that would impact on their management,
6 therapy or decision making in any way, shape or form
7 on the patient, so I was just questioning whether the
8 situation I see as an investigator in the field
9 looking back at Washington instead of being here in
10 Washington today is the idea that we essentially can
11 set up gene production facilities in many different
12 sorts of venues without any very high level of local
13 oversight except for perhaps approval by an
14 institutional, by a safety committee.

15 DR. FREY-VASCONCELLS: But I think if you
16 -- you have to understand that even if you're doing
17 investigational studies, you still have to follow the
18 GMP regulations. GMPs don't kick in at licensure.
19 They kick in when you're doing clinical trials.

20 DR. SALOMON: But a single center gene
21 therapy trial doesn't require production of the vector
22 in a GMP facility.

23 DR. FREY-VASCONCELLS: It's supposed to be
24 in the spirit of GMPs. I mean there are -- I know,
25 what's the spirit of GMP.

1 DR. SALOMON: Wash your hands in the
2 morning.
3 DR. FREY-VASCONCELLS: Yeah. I mean you
4 do have to follow the appropriate record keeping. You
5 have to be able to say at any point in time what you
6 did and how you made your product and how you tested
7 it. In testing, it may not be that you have a
8 validated test method, but you clearly have to have
9 run appropriate positive and negative controls to
10 ensure that your assay was working.
11 DR. SALOMON: So is there -- do we feel
12 that that is -- right now, basically, we're policing
13 ourselves then in the sense that we have our
14 institutional review committees, our biosafety
15 committees, our institution review boards and then, of
16 course, if we have NIH grants or we have a RAC
17 approval, etcetera, we have several different federal
18 agencies and an IND, then the FDA is involved. So
19 that's quite a bit of regulation. I agree.
20 DR. FREY-VASCONCELLS: Right.
21 DR. SALOMON: And the minute you become
22 multi-center it probably gets kicked up a degree. So
23 are we ever going to the point where we need to be
24 thinking about some sort of a qualification that goes
25 beyond just saying this is a GMP gene vector facility,

1 but this is a qualified gene vector production
2 facility and that would be something then at academic
3 centers would aspire to or perhaps would only be
4 community resources?
5 DR. FREY-VASCONCELLS: I think there are
6 discussions on that. The problem is the Agency
7 doesn't necessarily have the resources to do that at
8 this point in time and so I think that that may be --
9 I know there has been talk with ASGT to potentially do
10 something like that. In fact, a couple of weeks ago
11 we just had a manufacturing meeting for -- to let
12 people know what would be expected of them and I think
13 part of the oversight is related to the quality
14 assurance program that you set up. There are clearly
15 checks and balances that are built into the system and
16 that's another reason that normally we don't ask for
17 that information up front, but we have found that
18 there's a lot of misunderstanding of what an
19 appropriate quality assurance program is in the
20 responses that we received. And so it's clearly an
21 area that we feel that we need to do more outreach on
22 and we need to have that information up front in the
23 IND and we have in many situations have told people
24 that if you don't have appropriate checks and
25 balances, we're not going to allow the trial to go

1 forward at this point in time. And that's one of the
2 reasons we're asking for the information prior to even
3 you starting a clinical trial.
4 DR. SAUSVILLE: Dr. Salomon, one point
5 that I'd like to make in response to your question are
6 we setting up a certifying, if I heard the word. One
7 problem with the gene therapy field is that it's been
8 a very evolving process, rapidly evolving and I think
9 that's where the analogy with the CLIA laboratory
10 issue that you raised sort of breaks down. A serum
11 sodium is a serum sodium is a serum sodium. Where as
12 a viral gene product circa 1992 was different in many
13 respects than the type of things that I think the
14 industry is contemplating today.
15 So I would actually caution against making
16 standards for facilities and rather focus on products.
17 In other words, each product needs to have elements
18 that I guess are addressed by the GMP regulations and
19 by what's brought to each product both by the sponsor
20 and the Agency.
21 DR. SALOMON: Yes, I wasn't selling any
22 particular agenda. The CLIA I was just using as an
23 example of a certification of a lab. You could argue
24 still that we are taking these products and putting
25 them into patients and I could, for example, create a

1 plasmid, create or clone a viral producing cell line
2 with high titer and show that I had a high infectious
3 titer, show that I had biological activity and show
4 that it would target the appropriate cells and do the
5 safety, but in the end, if you went back through my
6 production facilities, it could be that it started off
7 in the hood in my regular room which was also doing
8 human, rat and pig studies and on and on and on, and
9 I didn't have full tracking of all the fetal calf
10 serum and other additives that were in the mixes. So
11 we have to be careful then that when -- I don't think
12 you can have alternatively your comment that we should
13 set standards for the product, we should just be
14 reasonable about the fact that the standards for the
15 product don't necessarily become standards for its
16 production.
17 DR. SIEGEL: Let me put a little
18 perspective here too regarding the analogies to CLIA
19 and other issues. If a gene therapy is being
20 manufactured for commercial use as a licensed product,
21 it will be regularly inspected and it will be licensed
22 which is a process I'm sure as rigorous as
23 certification of a clinical laboratory. So what we're
24 talking about here is experimental products and they
25 are held to good manufacturing practices. The concern

1 and the issue that Joyce was talking about in terms of
2 what she termed the spirit of GMPs is that the good
3 manufacturing practices, regulations, recognize that
4 they need to be phased in during certain, during
5 clinical development and the reason is that some of
6 them, some of the extensive validation and process
7 controls are appropriate when you're making thousands
8 or millions of doses, but are not appropriate for a
9 Phase I clinical trial in significant part because
10 they'd involve such an investment of time and effort
11 that no drugs would ever be developed.
12 So we require good manufacturing practices
13 appropriate controls to ensure even at the small scale
14 the quality, sterility, purity, potency of the
15 product, but some of the specific regulations,
16 particularly those involving validation, but others as
17 well, don't have to be met in the same way or in as
18 rigorous or detailed a manner as they do as one moves
19 through production. So it's a graded in -- it's a --
20 you know what I'm saying.
21 DR. SALOMON: I do.
22 DR. PATTERSON: I just have three brief
23 questions for Joyce. They're sort of overview
24 questions. One has to do with numbers, the second
25 with the cross referencing of master files and the

1 third with the process.

2 In your background material, you mention
3 that you received 200 out of 270 responses to the
4 letter. Could you speak about the fate of the 76 INDs
5 for which you didn't receive responses for or maybe
6 someone else will cover that. I just want to have an
7 understanding what the denominator is here.

8 The second question I have and I'm
9 confused and hopefully you'll be able to lead me into
10 the light. You mentioned that some sponsors cross
11 reference other INDs and/or master files and in cross
12 referencing these INDS or master files they are
13 relying on data, pre-clinical data, in particular
14 sometimes product manufacturing data. And you
15 mentioned also in the background materials that
16 sometimes these files don't contain the data that was
17 being cross referenced or relied upon. And my
18 question is how can that happen? How can an IND be
19 authorized if, first of all, it would be the sponsor's
20 responsibility to know if the data is truly there that
21 they're relying on and secondly, it would be the
22 review staff's responsibility to look at the INDs and
23 master files and make sure that the proper data is
24 there to support authorization of the IND that's
25 relying on it. So I'm -- I probably missed something

1 very fundamental in here, but I'm perplexed.

2 And then my third question has to do with

3 process. You're developing recommendations and

4 training and outreach and coming to the Committee here

5 for their very valuable insights and expertise. But

6 I'm wondering if at least some point today you can

7 talk about what the process is for outreach to the

8 broader scientific community and the investigators and

9 industry to I guess have a relative consensus about

10 how to achieve what are very, very laudable goals,

11 apart from today's deliberations.

12 DR. FREY-VASCONCELLS: Okay, to answer the

13 first question in relation to the number of INDs, the

14 responses we received were for active INDs. We felt

15 it was important at this point in time to bring INDs

16 where patients were actively being treated and studied

17 to today's standards. So we got -- we did receive

18 responses from a number of people who clearly

19 indicated that their file is no longer active. They

20 just had never bothered to inactive the IND. So

21 that's why a lot of letters went out and it actually

22 proved to be a very useful exercise for the Agency

23 because a lot of sponsors didn't realize they had

24 never inactivated the IND. So that's the difference

25 in those numbers.

1 As far as the master file, this is one of
2 those areas that actually is quite troubling to the
3 Agency. Generally, when we get a letter of
4 authorization for cross referencing, the letter says
5 that the sponsor, that the holder of the IND is
6 authorizing cross reference to a particular sponsor.
7 That's the limit of what we get. We don't know
8 exactly what they're authorizing. Now our regulations
9 clearly state that when you provide a letter of
10 authorization, you need to include exactly what
11 information you're authorizing that can be cross
12 referenced, the page numbers, volume numbers, where it
13 can be found. So that has been an issue for us is
14 when we get these global letters, what exactly is
15 being cross referenced?
16 The thing is is that a sponsor, the
17 purpose of a master file is so that we can use
18 information in the cross reference file to support an
19 IND and to be able to keep information proprietary.
20 So if you're a sponsor and you want to cross reference
21 something, no, you're not going to necessarily know
22 what is in that file. It may be proprietary
23 information and this is a mechanism by which it can be
24 used to support your IND. But like I say, the problem
25 is if you don't know -- if you don't clearly state

1 what's being -- what you're authorizing, it makes it
2 difficult for the Agency to make that assessment and
3 so you're right, we have had situations and that's one
4 of the things we found out in this is we had
5 situations where a sponsor was cross referencing a
6 file and they weren't on the same page as to what the
7 information was and it wasn't clear to us that they
8 understood. So it's something that we've been
9 clearing up through this process, outreach and other
10 activities.

11 DR. SIEGEL: Before you leave cross
12 referencing, I want to say something though about --
13 you asked about how would the clinical reviewer not
14 have picked this up. What we've discovered, in part,
15 is the IND comes in, it cross references the master
16 file, the clinical reviewer reviews the master file
17 and reviews the INDs. And there's adequate
18 manufacturing testing or preclinical testing. Now
19 it's three years later and we say have you done
20 changes in manufacturing testing or new animal studies
21 that you haven't told us about that you were supposed
22 to and the sponsor says yes, we have, it's in the
23 master file. And we look at the master file and it's
24 not there. So that's what they're talking about.
25 It's not that there was a deficiency in what was sent,

1 but that there was additional information that we're
2 asking since the IND went into effect that in some
3 cases sponsors thought were in the master file, but in
4 fact, weren't and it's part of this bigger issue of
5 sponsors not always knowing what's in the master file
6 and what has been submitted.
7 DR. FREY-VASCONCELLS: So in regards to
8 that what we are now actually doing is if we get one
9 of these global letters, we're not necessarily
10 accepting the global letters. We're going back and
11 saying no, we need to know exactly what you're cross
12 referencing.
13 MS. LAWTON: I have a question with
14 regards to the analysis of the responses. I know in
15 some of the specific questions responses to some of
16 the specific questions you look at the responses as
17 far as the different types of sponsors, for example,
18 is it sponsor investigator, was it industry sponsored,
19 etcetera. And I particularly on the manufacturing
20 side, I would like to know did you break down the
21 analysis into sponsor investigator, small company,
22 large company type situations to understand whether
23 there are any particular trends with your concerns
24 around the manufacturing facilities and the QA/QC
25 controls and whether that's something we should indeed

1 be looking at?

2 DR. FREY-VASCONCELLS: We didn't do a real

3 in-depth. It was more just an assessment as we were

4 going through. And to be honest with you, we didn't

5 find that there were really any issues related to one

6 that quote big manufacturers were doing things any

7 better than academic manufacturers.

8 The issues were the same across the board.

9 There didn't seem to be trends in that area.

10 Outreach. You're right. That's probably

11 one of the most difficult areas for us, but clearly

12 any recommendation that we put forward, it will be to

13 get -- to also get public input into those

14 recommendations.

15 DR. NOGUCHI: Although I have to say what

16 we're presenting here are our evaluation of what we

17 view as current safety issues and in terms of

18 implementing them I think there's ample room for

19 discussion, but in terms of discussing whether they're

20 important or not at this point in time, a large part

21 of what we're discussing are these are things that we

22 do think need to be implemented in terms of safety at

23 this early stage in gene therapy.

24 DR. SALOMON: Yes, I would go back to my

25 comment. When the staff showed me the questions and

1 the things that we were going to be talking about in
2 the next two days, again, my response was this is
3 probably one of the most important meetings we'd had
4 in a long time and given the potential impact to some
5 of these discussions we're going to have, I was
6 surprised that it wasn't standing room only of
7 sponsors, concern with how we were going to develop
8 things. That doesn't, by the way, mean that the
9 audience isn't still -- every person is important to
10 me. It's just surprising because of the global nature
11 of these things.
12 But I do feel, Amy, that you're bringing
13 up a point that everybody is sensitive to and I think
14 these are things that ought to go on to discussion at
15 big groups like PhRMA, the American Society of Gene
16 Therapy meeting in Seattle later in the year and I
17 think we need to, many of us involved in those
18 organizations should make an effort to bring them
19 forward so they are discussed there.
20 Joyce?
21 DR. FREY-VASCONCELLS: Actually, we do
22 every year have heavy participation at the ASGT and in
23 fact, there's going to be a two-day training session
24 on clinical trials and I don't know exactly -- I
25 haven't seen the latest agenda on that.

1 DR. SALOMON: It's sort of -- it's
2 basically a workshop on doing for clinical
3 investigators in how to take a clinical gene therapy
4 trial from beginning to the end with active
5 involvement with several FDA staff.
6 DR. FREY-VASCONCELLS: And I know other
7 years we've done training sessions, workshops on
8 manufacturing. I think this year we're going to try
9 and have a booth at the ASGT and so we're constantly,
10 and I know we have taken issues to the RAC for public
11 discussion. And so as much as we can, we try and get
12 out there to get our message and to get input from the
13 public.
14 DR. SALOMON: Abbey, did you have a
15 question and then we need to move on?
16 MS. MEYERS: In terms of something that's
17 been in the news lately which is upsetting the public
18 about these people who are claiming that they're just
19 going to go out and clone a human being and is there
20 anything to stop me from manufacturing gene therapy
21 vectors in my garage, since you don't have any
22 requirement for certification?
23 (Laughter.)
24 DR. SALOMON: In terms of giving them to
25 people are you suggesting or just making them?

1 MS. MEYERS: I'm talking about opening up
2 a gene therapy clinic in my basement which is what the
3 cloning people are claiming they can do. What is
4 there to stop me. I don't have to have a factory
5 approved by the FDA in order to make these things.
6 DR. SIEGEL: Yes, you do. You have to
7 have an approved IND with the FDA and you have to
8 submit the responses to all these questions and
9 extensive data about manufacturing and about your
10 clinical study plan before you get authorization to
11 proceed and to do otherwise would be a violation of
12 law.
13 DR. SALOMON: Abbey, let me clarify. It's
14 important that -- my questions were specifically about
15 the production facility. You took it another step
16 further and we're talking about actually giving it to
17 a human being. Once you want to cross that line then
18 all the existing regulations are fine. There's no
19 issue.
20 MS. MEYERS: It's the certification
21 question that I'm concerned about is you know, for
22 example, scientists who are developing genetic tests
23 for people with rare hereditary diseases, academic
24 laboratories don't have CLIA certification and FDA
25 could walk in and say we want you to stop developing

1 this test because it's not a CLIA lab. Several
2 government agencies can do that. But now you're
3 saying that gene therapy manufacturing facilities,
4 vector manufacturing facilities don't have to be
5 certified.
6 DR. NOGUCHI: But when we're talking about
7 certified from the FDA viewpoint, we license both
8 manufacturing and products at the same time, once
9 they're approved and have been shown to be safe and
10 effective. So that's our level of certification.
11 That means you can legally sell this and administer it
12 by a physician in the United States. Prior to that,
13 all our regulations for the pre-IND do pertain. If we
14 learn of deviations or of labs starting up in the
15 night, we will take appropriate action which in the
16 case if there is no IND that's associated with it, we
17 can shut them down, we can seize, we can move for
18 injunctions. There's a whole variety of things and we
19 would do that as a matter of fact. So certification
20 is not a necessary component for the FDA to take
21 action and to prevent illegal activities from
22 happening in this area.
23 DR. SALOMON: Well, themes of this can
24 come up later, but I'd like to move on here to Mary
25 Malarkey is going to talk about the QC/QA analysis.

1 MS. MALARKEY: Good morning. That was a
2 lively discussion on that topic. As Dr. Frey said,
3 Item 5 of the Dear Gene Therapy Sponsor letter caused,
4 we believe a lot of confusion, that is, what is the
5 expectation for Phase I in relation to quality.
6 In addition, I'm going to speak very
7 briefly on multi-use contract facilities because
8 that's another area that causes a bit of confusion.
9 That is if a sponsor contracts out the manufacture or
10 testing and/or testing of their product, what are
11 their responsibilities and what are the
12 responsibilities of that contract manufacturer?
13 Next slide, please. Quality is a GMP
14 expectation. That is under Title 21 of the Code of
15 Federal Regulations, Parts 210 and 211. It is
16 expected that a quality unit will be in place. Once
17 you prepare product for administration into humans,
18 then technically speaking, the GMPs fully apply.
19 However, as has been mentioned by Dr. Siegel and Dr.
20 Frey, we have looked at this as a step-wise approach.
21 Certainly, there are certain GMPs that are expected
22 right from Phase I, but things such as validation and
23 end process controls develop along with the product.
24 Another point of confusion, good
25 laboratory practices are not GMPs. The GLPs are

1 specific to pre-clinical studies. The GMPs cover all
2 phases of manufacture, controls and documentation as
3 well as testing. One thing the regulations do not
4 make the distinction of is the difference between
5 quality control and quality assurance.

6 Next slide. Under 211.22, the quality
7 control unit is defined and the first three bullet
8 points here really are more of what we look at today
9 as quality assurance, keeping in mind that the GMP
10 regs were published in 1978, so expectations have
11 changed over time. The quality assurance function is
12 to approve and reject all components, intermediates or
13 products, to approve and/or reject all of the
14 procedures that are used and the specifications, to
15 review all the records for a given lot of product to
16 ensure that it meets the specifications and if there
17 are deviations that investigations are performed to
18 try to find where the problem lied and to correct that
19 problem so it doesn't recur.

20 The fourth bullet here is more what we
21 think of as QC today and that is the laboratory
22 function, the actual testing function. And all the
23 responsibilities, regardless of whether it's QC or QA
24 are expected to be in writing.

25 Now the last bullet here is not in the

1 regulations, but it's become an industry standard and
2 an Agency expectation over time. And that is that the
3 quality unit needs to be separate from production and
4 this is the system of checks and balances, so there
5 isn't a conflict of interest between the people
6 manufacturing the product and actually releasing the
7 product to the public.

8 Next slide, please. In 1996, there was a
9 proposed revision to the 211s and industry asked that
10 the Agency define quality assurance and quality
11 control. At that time the Commissioner, Commissioner
12 Kessler said that we don't really care what you call
13 your unit as long as you have the functions that are
14 needed. So as I said earlier, quality control has
15 generally evolved to mean the testing activities to
16 ensure that the specifications are adhered to whereas
17 quality assurance is really the oversight
18 responsibility, really the QC of QC, if you will.
19 This unit is responsible for auditing all the methods,
20 the results, the systems and the processes and
21 trending of data to show where things are starting to
22 get out of a state of control.

23 Next slide, please. The next couple of
24 slides go into some other regulations that give
25 quality definitions. In the GLPs, we have a quality

1 assurance unit definition and at the very end of that
2 you can see that it talks about being entirely
3 separate from and independent of the person engaged in
4 the conduct of the study.
5 Next slide. The proposed rule for the
6 Good Tissue Practice Regulations which is a fairly
7 recent publication defines a quality program and this
8 is where we see the terms preventing, detecting and
9 correcting deficiencies and this is, of course, the
10 language that was in item 5 of the Dear Gene Therapy
11 Sponsor letter.
12 We understand that there are some unique
13 considerations for these products, particularly in
14 Phase I and Phase II. That is, the QC unit and the QA
15 unit may be one person as opposed to in a
16 manufacturing facility where you would see a whole
17 unit of people devoted to these tasks. Most QC, that
18 is the testing function may, in fact, be contracted
19 out, so the sponsor may not have a QC unit per se.
20 Validation and qualification activities may also be
21 contracted out and many vendors are involved, that is,
22 rather than manufacturing media or putting in a
23 pharmaceutical water system, these may be purchased
24 already pre-made.
25 And in the case of the National Gene

1 Vector Labs we have a situation where we have multiple
2 sponsors that are using the same facility or having
3 products manufactured in the same facility.
4 Next slide. The most general
5 consideration with quality is documentation.
6 Everything needs to be documented and this is an
7 expectation right from the very beginning. It is
8 understood that these procedures will evolve over time
9 as the process evolves. However, batch production
10 records are a requirement. This is every step in the
11 process is documented along the way. The equipment,
12 the cleaning and use of the equipment, what lot of
13 product was in the particular piece of equipment on a
14 given day, laboratory records, standard operating
15 procedures are basically procedures that go to
16 everything that is done within a given facility.
17 Distribution records, which I have here in quotes as
18 the distribution may, in fact, be just right down the
19 hall in the hospital setting to a patient if it's a
20 direct vector or cell product.
21 And finally, complaint files are something
22 to start thinking about, if in fact, you are a
23 facility that is multi-use and is actually
24 distributing product to other people.
25 And the main point here is that adequate

1 documentation allows traceability, so if there is a
2 problem, you're able to find where the problem lies
3 and hopefully to correct it.
4 So going through the letter or that item
5 in the letter, the first bullet was preventing
6 deficiencies. And of course, this is the most
7 important thing. If you can prevent deficiencies from
8 occurring in the first place, then you're far along
9 the way. These are some examples of things that would
10 be preventive measures. Of course, testing of all
11 cell and viral banks. If you aren't doing that
12 testing yourself as a sponsor, it's expected that you
13 will review all the SOPs that are used, any validation
14 protocols for the assay methodology, and of course,
15 all the results that are obtained from the test lab.
16 Testing or certification of components, I
17 just give one example here, of course, of our concern
18 with bovine-derived materials and certifying that they
19 are from BSE-free countries. And screening of
20 patients or if you don't choose to screen patients, if
21 you're using cells of multiple patients in your
22 facilities, then one would expect that you would use
23 universal precautions, that is, just assuming that
24 there is everyone is potentially infectious or every
25 cell line is potentially infectious.

1 The facility, there's been a lot of
2 discussion about the facility itself. We do expect
3 that it would be adequately designed and validated for
4 its intended use. The equipment needs to be
5 calibrated, qualified and certified. There should be
6 maintenance and monitoring procedures to ensure that
7 the facility maintains the state of control and
8 requalification, recertification, recalibration
9 activities should be in place.
10 Cleaning becomes extremely important,
11 particularly with multi-use facilities and we
12 recommend a variety of cleaning agents be used because
13 no one agent is effective against all potential
14 organisms that one may encounter. And segregation is
15 extremely important as well and this is a
16 cross-contamination prevention issue.
17 Finally, the manufacturing process itself
18 and this could be, of course, the vector or when I say
19 product here I mean if it's cells or the actual
20 product, controls need to be developing and again,
21 Phase I and II, we don't expect full controls to be in
22 place but towards Phase III and then into licensure
23 it's expected that in-process testing will be
24 performed and specifications set.
25 Validation of aseptic processes, on the

1 other hand, is an expectation right from Phase I.
2 Sterility is extremely important and if you're doing
3 aseptic processing, that is, after filtration or not
4 able to filter a particular product, then it's
5 expected that you will validate, that you can maintain
6 aseptic conditions during its manufacture. Operators,
7 of course, need to be adequately trained and qualified
8 for their intended tasks and you need to have
9 procedures to look at deviations when they do occur.
10 And finally, of course, the testing of the
11 product and review of all records associated with the
12 lot need to be done prior to release of any given
13 batch.
14 Some detection considerations, monitoring,
15 of course, of the facility as well as the personnel.
16 This is environmental monitoring as well as monitoring
17 of temperature, humidity, pressure differentials,
18 whatever is important to maintain that state of
19 control. Testing, not just of the final product, as
20 I said, but components, everything that's going into
21 the product as well as starting to set up some
22 in-process tests. And finally, I mentioned trending
23 before. It's not specifically a requirement, but it's
24 a good idea in order to demonstrate that you're
25 maintaining control over time.

1 When problems do occur and even in the
2 best of circumstances they do, you need to think about
3 what to do to correct them and this is the importance
4 of traceability and all the documentation that I
5 mentioned earlier. You need to have procedures in
6 place for performing an investigation. What are you
7 going to do? What are you going to look into? What
8 data are you going to review? You should have an idea
9 of what corrective actions you may think of performing
10 if you do find the problem and of course, procedures
11 for handling of complaints or any adverse events that
12 are tied to manufacturing. And finally, procedures
13 for notification of physicians, patients, FDA, all of
14 these components.
15 The letter also asks for an identification
16 of authority and this is really the important checks
17 and balances issue. Again, the quality unit should be
18 separate from production and of course, production is
19 sometimes the sponsor themselves. This quality unit
20 has to have the ultimate authority to release or
21 reject so they can't both be producing and testing and
22 reviewing and releasing. Again, we have a conflict of
23 interest there. The ideal situation is a separate
24 unit with ultimate reporting to the sponsor, but the
25 authority to basically override the sponsor and this

1 is a difficult concept and we understand that, but
2 even in a licensed manufacturing facility, we don't
3 expect that the CEO would be able to override the
4 quality unit decisions.
5 There was also a request for the date of
6 the last audits that were performed. Of course, this
7 suggests that there needs to be a plan in place for
8 audits, what you need to audit, how you're going to
9 perform an audit and the frequency of your audits.
10 Under the regulations, it's required that
11 an annual review of your manufacturing operations for
12 each given product be performed. This would be a
13 representative number of batches. All associated
14 records of those batches and after that review is
15 complete and compiled, it needs to be reported to the
16 responsible individual. So if the quality unit was
17 doing this, it would then report those results to the
18 sponsor.
19 Vendors, we understand there could be a
20 lot of vendors involved and I think at Phase I-II, the
21 expectation is that you'll get a certificate of
22 analysis, but over time you need to start putting some
23 testing into place, not just relying on the C of As.
24 The contract validation activities, again,
25 the validation of a facility is a difficult task and

1 not often can be done in an academic setting. So once
2 you -- if you have people come in to help you validate
3 a facility, for example, you need to be involved and
4 you need to pick up the ball so that you can maintain
5 that facility or that validated state.
6 And finally, contract manufacturers.
7 Years ago this was generally testing, so the cell and
8 viral bank testing is contracted out. Even most final
9 product testing is contracted out, but again the
10 quality assurance function of the sponsor in this case
11 would be reviewing and approving all the SOPs that are
12 used, validation protocols that are used and
13 reviewing, of course, the test results. But we're
14 seeing more and more where the entire manufacturing
15 process is being contracted out. And often, it's
16 being -- the products are being manufactured in
17 multi-use facilities and this brings up some questions
18 as to who is responsible for what.
19 The bottom line is the sponsor is
20 ultimately responsible for the quality of the product.
21 So again, review and approval of all relevant
22 procedures, including product testing, all the data
23 generated during production and testing would apply.
24 And this is again the QA oversight function. Even if
25 you're not the manufacturer. Now we also recognize

1 that many sponsors may perform some specific testing
2 and not contracted out, such as potency. If this is
3 the case, then you have the QC function.
4 And finally, if you are contracting out,
5 it's expected that you will have enough information on
6 other products that are being manufactured to evaluate
7 all the cross contamination procedures that are in
8 place. So there may be proprietary information. That
9 is the exact products that are being manufactured, but
10 you need to know enough about them to know that the
11 cleaning procedures, etcetera are appropriate and that
12 your product will not become contaminated.
13 Now the contract facility also has
14 responsibilities and of course, the main one is they
15 need to operate under appropriate GMPs. They're also
16 usually the ones responsible for validating the cross
17 contamination prevention procedures and this would be
18 such as cleaning procedures and we don't have any
19 current expectation on how this will be performed. We
20 are certainly open to review data and make
21 suggestions. This is a very interesting topic and how
22 you demonstrate that you're not contaminating one lot
23 of product with another or one vector with another.
24 And finally, the contract manufacturer may
25 submit a Type V Drug Master File and in this file they

1 may put all the proprietary information that they do
2 not want to share with the sponsors that are using
3 their facility or having their product manufactured in
4 their facility. We did away with Type I Drug Master
5 Files last year. This was the historic --
6 historically, that's where this information would be,
7 but now we're saying you can submit a Type V without
8 prior permission from the Agency.
9 So in conclusion, sponsors should be in
10 compliance with GCMPs with respect to these quality
11 functions and we do have these special considerations
12 that we're getting more and more concerned about for
13 multi-use facilities. But keep in mind that the
14 sponsor does have the ultimate responsibility for
15 product quality, but that the contractor also has
16 responsibilities which is adherence to GCMPs and
17 validation of cross-contamination procedures.
18 Thank you.
19 DR. SALOMON: Mary, can you clarify, I
20 just don't understand the difference between a Type I
21 and a Type V Master File?
22 MS. MALARKEY: Okay, yes. Master Files
23 are defined in 314, 420. There are five types or
24 there were five types. The Type I was specifically
25 for facility information. And this was done away

1 with. Generally, mostly CBER using the Type Is. The
2 Type V is kind of the catch all for everything that
3 doesn't apply or doesn't fall into the II, III, IV
4 category. And the regulation does say that you need
5 to get prior permission from the Agency to submit such
6 a file. But we are saying for certain circumstances,
7 we will accept one without that prior permission.
8 I hope that helps.
9 DR. SALOMON: So I'm just not sure what
10 would be in the Type V. In the Master File, for
11 example, let's say I had a proprietary viral producer
12 cell line or a helper system or something like that.
13 Is that what you're talking about?
14 MS. MALARKEY: No, what I'm talking about
15 --
16 DR. SALOMON: Or verification or viral
17 concentration?
18 MS. MALARKEY: I'm talking specifically
19 the facility. So if I'm a contract manufacturer and
20 I manufacture multiple sponsors' products, then I
21 could submit a Type V Master File with my facility
22 design, my diagrams, the flows, the SOPs, the general
23 SOPs that are in place, as well as a list of those
24 products, specifically that I manufacture, because
25 again, that information would not necessarily all be

1 shared with the sponsor.

2 DR. SALOMON: So just to follow up on

3 that, I mean in a number of different kinds of gene

4 delivery vector systems, there are standard quote

5 unquote cell lines or helper cell lines or various

6 things depending on whether you're talking about the

7 adenos or plasmids or retroviral vectors. That you

8 could do multiple kinds of studies by inserting in the

9 gene of choice is plasmid and then you deliver it with

10 these proprietary vector-producing lines. Where would

11 they be? The production facility could control these

12 GMP level producer cell line systems.

13 MS. MALARKEY: Yes, as I mentioned, there

14 were Types I, II, III and IV and I believe that this

15 would fall into a Type II Master File.

16 DR. SALOMON: Any other questions?

17 Richard?

18 DR. MULLIGAN: I'm interested in the

19 cross-contamination issue. When you looked at the

20 contract facilities, I would find it hard to believe

21 there's almost any contract facility that actually

22 would do the direct sorts of cross-contamination

23 tests, so were there cases where, for instance, people

24 making an adeno vector and retrovirus vector actually

25 looking for retrovirus vector, not just a generic

1 retrovirus, but retrovirus in their adeno, perhaps,
2 and other than doing those direct sorts of tests, it's
3 not clear how you'd really ensure that there's not
4 cross-contamination.
5 MS. MALARKEY: That's a very good point.
6 And that's something we are all struggling with and I
7 think what I'm talking about here is more
8 demonstration, not product testing, but actual
9 cleaning validation, really, equipment and facility
10 validation of the cleaning processes as opposed to
11 testing one lot of product for another type of
12 product, so to show that your cleaning processes are
13 effective in removal. There are other things such as
14 using different pipetters or other controls that can
15 be put into place to ensure that cross-contamination
16 won't occur.
17 DR. MULLIGAN: Is it fair to say that, in
18 fact, there hasn't been any case where people have
19 done these direct tests as far as you're aware?
20 MS. MALARKEY: No, I don't believe that
21 that is the case. Dr. Epstein?
22 DR. EPSTEIN: There are some cases, for
23 example, it's not the one that you're talking about,
24 but we're asking for PCR looking for the wrong
25 plasmid, the previous one. And we're asking a lot of

1 questions about dedicated equipment, that changing of
2 tubing and so on. So sometimes we directly as-test
3 for the product before yours.
4 DR. MULLIGAN: A more general question is
5 this issue of what it means for the sponsor to be
6 responsible for production, if it's a contract
7 facility. What is the -- can you give a better sense
8 of what you can possibly mean as being responsible if,
9 in fact, you don't have a lot of proprietary
10 information about things that are going on in the
11 facility that are likely to cause contamination.
12 MS. MALARKEY: Well, the
13 cross-contamination issue is certainly a separate one
14 and it does involve proprietary issues of its own.
15 However, if you are contracting out your product to be
16 manufactured, then our expectation would be that you
17 would review all the batch reviews, that is the blank
18 records up front, you would approve -- you would
19 ensure that, in fact, the facility was doing the
20 production as they should, in addition to all their
21 standard operating procedures and those types of
22 things would have to be reviewed. I mean you would
23 want to know how your product is being produced, what
24 testing is being done, what procedures are in place to
25 prevent not just cross contamination, but

1 contamination of the product.

2 DR. MULLIGAN: I think that there's many

3 cases where there's a very non-industrial investigator

4 who is getting product from a company because, in

5 fact, they don't have the expertise to know what a

6 batch record is from whatever is. And the question is

7 whether or not you actually have the expectation that

8 an investigator would have enough expertise in these

9 specific areas to actually be capable of reviewing the

10 manufacturing process.

11 MS. MALARKEY: Well, it may not be the

12 investigator themselves, but someone that they have on

13 their staff that would be that quality person that

14 we're talking about. I understand exactly what you're

15 saying, but you do need to be concerned as an

16 investigation and if you aren't, if you don't feel

17 able to do that, then you need to have a quality

18 person in place to do those types of functions and

19 that's where we're seeing problems. There isn't that.

20 There isn't the responsibility being taken and there

21 are problems in that area.

22 DR. SALOMON: Michael and then Dr.

23 Sausville.

24 DR. O'FALLON: The presentation was

25 actually overwhelming as far as my sense of the

1 complexity of the entire thing and you've just hit on
2 one of the areas where that's almost certain to fail.
3 I mean one of the basic tenets of modern quality
4 assurance is the more complicated you make things, the
5 closer you are to having the probability that one,
6 that something will go wrong. I was really awed by
7 your presentation and by the fact that there are so
8 many different things that we are trying to control
9 here. This is an observation, not a question, nor do
10 I have a solution to it, but I can imagine the guru of
11 modern quality, Deming, is probably turning over in
12 his grave as he tries to imagine how we could handle
13 this and it is so critical. I agree completely with
14 our Chairman's earlier comments. It is so critical.
15 Just setting up more rules and regulations is not a
16 solution to that problem.
17 DR. SAUSVILLE: Yes, and picking up on
18 that and also on Dr. Mulligan's comment, I think it
19 illustrates the point that was made previously that
20 trading and outreach as this field evolves is really
21 going to be an absolutely critical function because on
22 the one hand, the innovation that gives rise to many
23 of these products does clearly originate in academic
24 settings. And we have encouraged often as part of the
25 illusion of that innovation that the academic

1 investigator take the lead in actually developing a
2 product to clinical trial.
3 On the other hand, though, I think what
4 we've heard today and I commend Mary Malarkey for
5 really going very lucidly through a complex area is
6 the -- something in our experience, academic
7 investigators, they just don't get it. When you start
8 talking to them about issues of quality control and
9 quality assurance, they fall asleep, they're not
10 interested. It's not something they've been trained
11 to do and I think that this is absolutely key. And I
12 actually believe that it also impinges on the doing of
13 science because ultimately, the scientific experiment
14 which is the early phase clinical trial, you need to
15 know what you have that has given you the result that
16 you're going to interpret and move on. And that's
17 really what quality control and quality assurance
18 gives rise to. So without, and again, this is more in
19 the spirit of an observation. I think this
20 underscores the training in outreach. I think that if
21 we're going to have and we should actually encourage
22 academic investigators to be active and viable in this
23 area, we -- the greater we, that is, NIH, FDA, the
24 people who are entrusted by the public with promoting
25 this enterprise, need to put in place the support for

1 investigators so that they feel they're empowered to
2 make these types of decisions and whether they want to
3 get involved. Because I think as the recent tragic
4 events have proven, we want to create a scenario where
5 recognizing there are going to be errors, there are
6 going to be problems. When you say a probability of
7 one, yes, that's right. Errors do happen. We have to
8 have in place an orderly and systematic way to
9 understand where the errors come from and have the
10 academic investigators buy into a ready participation
11 in that process. I'm sermonizing, but I think that's
12 what we have to do.
13 DR. SALOMON: I'm kind of enjoying this
14 because that was exactly what I was thinking and of
15 course, I have the advantage of having seen this stuff
16 a little bit ahead of you and that was where my
17 comments were coming from. I mean the way I'm
18 thinking about it and trying to take what I've heard
19 just in the last few minutes and make it, think about
20 it in a constructive way, is that we have issues, of
21 course, where we have a lot of different companies
22 that I think are much -- that have vector and viral
23 production facilities and they know what they're
24 doing. They come from an industrial culture. They
25 understand what a GMP facility is. Oftentimes, they

1 already have existing GMP facilities and they've just
2 taken over a part of them, so that they have very
3 sophisticated QC and QA and they know how to deal with
4 the FDA, etcetera. But then we have a whole other
5 world. I think that's where Dr. Mulligan and Dr.
6 Sausville and myself are coming from when we're saying
7 there's a lot of stuff going on outside our labs.
8 We're talking about setting up an GMP facility at
9 Scripps for islet isolation and for gene therapy to do
10 our own trials and there it gets really very
11 complicated because even in a grant, I know my first
12 version of my NIH grant for gene therapy they cut out
13 two of the technicians because they were well, you
14 know, Dr. Salomon doesn't need that technician to do
15 this trial and that's where -- there would be your
16 quality control, they were supposed to be data
17 monitoring technicians and they cut them out of two of
18 the centers in the trial.
19 (Laughter.)
20 DR. SAUSVILLE: So that illustrates the
21 lesion, okay. Because you create a situation where
22 it's really impossible for the academic investigator,
23 even if you, in your particular case you plan for it.
24 So one interpretation which some have given is that's
25 a reason why academic investigators in a sense

1 shouldn't play in this game. I don't hold that, but
2 you could take that as the limit case.
3 On the other hand, as I stated
4 emphatically, innovation in this field comes from
5 academia in the main. It is brought to fruition
6 certainly by the industrial sector, but I think we
7 have to define a set of rules of engagement that allow
8 facile participation by academia.
9 DR. SALOMON: I totally agree with that
10 and so I think that therefore some of where we could
11 start would be creating a couple focused places where
12 you could go if you were in an academic institution
13 and get first just some real education in it. I know
14 when I did it, I was very fortunate, I happened to be
15 able to call Phil and Joyce and Amy and they were kind
16 enough to spend some time taking my ignorant self and
17 educating me about what I needed to do. Oh yes, you
18 might have to go in front of the RAC, thank you, Amy,
19 that kind of stuff.
20 (Laughter.)
21 But that's not really very efficient. So
22 perhaps the first thing that we ought to be doing is
23 setting up sort of a website area that might be a
24 collaboration between the FDA and the RAC, the NIH,
25 where you could go and there might be then if you have

1 further discussions you could call these people to get
2 sort of specific answers by e-mail. I'm not saying
3 that everyone has to be running around with cell
4 phones to know that this is an emergency.
5 I think that there ought to be some sort
6 of --
7 DR. SIEGEL: Those -- we have those
8 websites. There are extensively and recently updated
9 websites at CBER and FDA with pages for clinical
10 investigators, pages for sponsors, phone numbers,
11 e-mails, whatever.
12 DR. SALOMON: Specific for gene therapy?
13 I guess that's what I was kind of saying, Jay.
14 DR. SIEGEL: Single site.
15 DR. NOGUCHI: It's evolving for gene
16 therapy. We have a site, but these types of
17 information you're talking about are precisely the
18 feedback that we are already getting and we're going
19 to be implementing.
20 DR. SALOMON: Jay, what Ed and I are
21 saying is that yes, I know, again because I've just
22 been educated by you guys that I can go to the FDA
23 websites and you can go through there and find, for
24 example, what's a good laboratory practice, what's
25 good manufacturing practice, etcetera, etcetera. But

1 if you're not in that culture, if you're not thinking
2 that way, I wont' necessarily know where to look and
3 what's relevant if I want to set up a gene therapy
4 development -- that's all I'm thinking about and I
5 don't have that sort of culture in academia. Maybe I
6 should if I want to get into this area.
7 DR. NOGUCHI: I'd like to just comment on
8 the comments to say that in a way, yes, this is a
9 critical moment for the field of gene therapy, but to
10 also offer the other side of it is yes, it is very
11 complicated, but many things are complicated. We
12 didn't put a man on the moon without a lot of
13 complications and science was the beginning, but
14 hardly the mechanism by which we get there. And
15 that's what we're talking about here.
16 The idea, the demonstration that an idea,
17 that a vector may have an approach is the easy part.
18 We're talking here about the very, very hard part,
19 hard because it's hard to get a hold on, hard because
20 it is not -- it is not rocket science, but it's very
21 much in the course of how do you assure to the best of
22 your ability that every trial being done is of the
23 highest ethical, highest scientific quality and has
24 the best chance for success. It can be done. It does
25 need a commitment and an understanding by everyone

1 here and throughout the academic and industrial
2 community that yes, we can do this. We just have to
3 commit to it.
4 If you were a cook, a gourmet cook, you
5 would be assured that you would know everything that
6 came into your kitchen and if anybody got sick, you
7 would be devastated. You might even close your
8 restaurant for just that. This is no less the same.
9 We're talking about quality. It is achievable. It is
10 do-able. It is work. But I am positive and FDA is
11 positive and the reason we're holding these kind of
12 conferences is to just say, yes, it's complicated, but
13 you can do it. We can all do this.
14 MS. LAWTON: Can I just follow up on that,
15 Phil, with a question? Obviously, the education piece
16 is a critical component here, but given the
17 presentations and what we're hearing is that this is
18 being an issue identified from the responses.
19 What is the FDA's perspective at the
20 moment around the compliance side and how you are
21 going to monitor? You said, for example, in new INDs,
22 you're going to be asking questions about the QA/QC.
23 Will you put INDs on clinical hold unless they have
24 those appropriate answers and then also, a second part
25 of that is are you expecting to up the number of

1 audits, the compliance side of things to make sure
2 that you identify and things are corrected in areas
3 where there are issues?
4 DR. NOGUCHI: In regards to the first
5 part, yes, we are considering that the answer to these
6 questions are a part of your IND submission and are
7 part of the information that we need to ensure safety.
8 If you don't provide the information or we feel that
9 it's inadequate, we will put the trial on clinical
10 hold until they're addressed.
11 In terms of the specific audits, this last
12 year, doing the -- what you will hear later on as
13 roughly 15 percent of active INDs, actually was an
14 enormous strain not just for our CBER compliance
15 people per se, but for the entire FDA inspection team.
16 We were able to do it in a relatively short amount of
17 time. We don't expect to be able to do that
18 continually, however, we will have through -- in the
19 future we will have a smaller number of audits of gene
20 therapy trials, very likely not nearly as many as
21 we've had, but yes, we will continue to have some spot
22 checking to make sure that things are going. But a
23 large part of it is going to be in terms of being up
24 front. This is the information required. Part of it
25 is also trying to expand the infrastructure of people

1 who are qualified to do these QA and QC types of
2 roles. There are not very many of those types of
3 people and yet obviously they are critical to the
4 whole enterprise.
5 We know of several cases in academic
6 institutions where literally a one QA/QC person is
7 being bid for and has his choice of going to Harvard,
8 St. Jude's, Baylor, any of the major institutions. So
9 a large part of where we think industry and academia
10 could help is programs to actually train people who
11 understand this and who live and breathe this and make
12 it sure that it becomes a viable career for people.
13 Right now, most of these people, other
14 than in the areas of high demand like in gene therapy,
15 they're sort of looked down on, well, you know, you do
16 QA/QC, yet, they're the heart and soul of getting
17 these products to the patient.
18 DR. CHAMPLIN: It's obvious, I think, to
19 everybody doing it that there's two major areas.
20 There's the gene vector production which is very
21 different than the center that is administering the
22 gene therapy therapy, so often the vector is produced
23 by a company and then shipped to the hospital where
24 the self-processing laboratory will actually do the
25 transduction of cells ex vivo, for example, and then

1 administer those to the patient. So the QA/QC issues
2 are obviously very different for the manufacturing of
3 the vector and the clinical approach to individual
4 patients. And I would view it that one would probably
5 not need quite the same level of QA/QC rigor in
6 dealing with the individual patient on the treatment
7 end, perhaps, than producing a vector that's going to
8 be given to thousands of patients by the manufacturer.
9 At least, it's a very different type of process that
10 needs to be considered.
11 DR. NOGUCHI: That actually is one reason
12 why if you look at the current good manufacturing
13 practices, they are not proscriptive in the sense of
14 you must have a person in QA/QC who has four years of
15 college and has been certified by X number of people.
16 We allow for local approaches to how you actually
17 address the issues that are there. It's true that the
18 complexity may be somewhat different for a single
19 patient versus the breadth of the field, however, we
20 do expect that at the very least, if you listen very
21 carefully, documentation, documentation and then
22 again, documentation is where you start.
23 Again, as Mary has pointed out, we know
24 something will go wrong at some point. This is
25 experimentation. We're talking about experimental

1 products. That happens. But you want to make sure
2 that if it happens, it happens once and not twice.
3 The way you do that is to have the documentation
4 regardless if it's for a single patient or for
5 thousands or hundreds of thousands of patients. How
6 do you prevent an accident that you know about from
7 every happening again? How do you learn how to do it
8 better? You have to document that.
9 DR. O'FALLON: A comment -- in the
10 academic environment we commonly refer to QA, whatever
11 terms we want to use frequently falls in the hands of
12 technicians as we've just heard you losing your data
13 clerks and your concept of independence is absolutely
14 ludicrous in that setting. Those people have no
15 independence whatsoever. Indeed, if they report
16 something they may get shot as the messenger who has
17 reported the bad news. And of course, one final
18 observation, this is much more complicated than rocket
19 science, we haven't sent anybody to the moon for a
20 quarter of a century and if we have a catastrophe such
21 as the Challenger in this arena, it will set this
22 whole business back I don't know how long, but a long,
23 long way. So this is extraordinarily important stuff.
24 DR. SIEGEL: Let me just say with the use
25 of terminology being a little bit confusing here,

1 there's a couple of issues I want to address. Dr.
2 Champlin, your comment about the importance of QA and
3 QC for the single patient, I assume is directed to the
4 issue of QA and QC over manufacturing of a product for
5 a single patient. The concept of QA and QC over the
6 treatment of the quality of the clinical trial and the
7 treatment of an individual patient is a critically
8 important and under appreciated concept that we'll be
9 discussing this afternoon. And indeed, the issue of
10 the independence of those processes and how you
11 monitor a clinical trial independently from the
12 investigator is an issue that's every bit as
13 complicated and I would hope not to use the word
14 impossible, but let us say complex and difficult as
15 the issue of how you QA and QC manufacturing
16 independent of the actual people doing the
17 manufacturing. I think we use the word independent as
18 a gray scale term rather than a black and white term
19 when we talk about these things.
20 DR. SALOMON: Comment from Amy and I'd
21 like to quickly summarize this. I'm going to try to
22 make an executive decision. We're supposed to have a
23 break at 10:30 and Carolyn hasn't had her --
24 introduced the idea of the Replication Competent
25 Retrovirus.

1 So what I'd like to do is have a comment,
2 summarize this really briefly and then ask Carolyn to
3 come up and talk, so we'll delay the break just a
4 little bit, if that would be okay with everybody.
5 Is that okay, Carolyn? Does that work for
6 you?
7 Okay, Army?
8 DR. PATTERSON: Three very quick things.
9 I thought that Dan, our Chairman, raised a very
10 important point about having something up on the web
11 that would essentially really walk people through in
12 addition to the various, somewhat complex, but very
13 critical guidances that FDA has up on their website.
14 And a suggestion I'd put forward is that the workshop
15 at ASGT and any further workshops not evaporate after
16 the workshop is over, but rather a set of facts,
17 frequently asked questions that come out of that
18 workshop could be put up on the web.
19 The second point, and I think Jay started
20 to address this, I want to make sure it's clear for
21 the public record the point raised by Dr. Champlin.
22 It is just as critical for single patient as it is for
23 large studies that involve multiple patients to make
24 sure that the product that is administered to the
25 patient is appropriately screened and tested. I think

1 that there are larger issues of complexity when one
2 moves from small scale to large scale production, but
3 I don't want anyone to leave this room thinking that
4 there's a lesser standard for small single patient
5 studies as compared to larger scale studies.
6 DR. CHAMPLIN: My point isn't that it's
7 less important, but it's clearly different. The
8 problems related to manufacturing a vector is very
9 different to the problems related to running a
10 self-processing facility where you're treating a
11 series of patients with transplants of various types,
12 some of which may be genetically modified and how
13 basically to regulate your practice environment of the
14 cell processing laboratories is totally different
15 issues than in the manufacturing of any sort of
16 product.
17 DR. SALOMON: Well, just by virtue of just
18 a quick summary here to make sure that we sort of give
19 everyone is on the same page on this, what I've heard
20 pretty consistently here is that there's generally and
21 I hear it also from the FDA staff that one of the
22 things that came out of the letter and reporting is
23 that things aren't so bad out there, that the quality
24 of the understanding in most of these vector
25 production facilities is very high and that reflects

1 I think a tradition in this country for GMP facilities
2 that is just being used now for gene therapy
3 production, but has been long out there and validated
4 and every -- a lot of expertise out there.
5 What I also hear us all saying is that in
6 gene therapy just as in any brand new cutting edge
7 technology, the contributions and the ability to
8 contribute actively by academic centers is critical
9 and there, things get more difficult because the
10 culture in an academic center is very, very different,
11 obviously, than that in industry. And the problem
12 then is that sponsors, including those at the table,
13 are not -- and we're probably a lot more sophisticated
14 through our interaction with you, are not, in general,
15 going to understand and/or appreciate these critical
16 details of QA and QC and GMP and GLP and cross
17 contamination and validation and that more education
18 needs to be there, a higher level of appreciation at
19 the level of the NIH study section needs to be there,
20 education of the faculty needs to be there and I think
21 two key points here came out. The one key point from
22 Drs. Mulligan and Champlin was just if you don't --
23 you've got to understand that what happens now is if
24 a sponsor is going to send out something and get back
25 their gene therapy product to deliver, that they're

1 going to do and I think that's what Dick and Rich
2 Mulligan were talking about, when that happens,
3 they're not going to really understand the intricacies
4 of going back on all the lot release forms that they
5 get in some big packet because their face is going
6 forward to the bedside or to the cell processing
7 laboratory. That's a real issue, I think, from the
8 point of view of the simple statement the sponsor is
9 responsible. So I mean I think if we want to hold
10 investigators in a system in which we're going to be
11 sending a lot of this stuff, then there really has to
12 be some serious education in the academic centers in
13 order for that to be fair because if a disaster
14 happens, I can just tell you right now, that these
15 guys, in general, are not going to go through all this
16 by just innocence. They're not going to realize it.
17 The other thing, I think, is what Ed said
18 and -- Ed Sausville -- and that is if you do a trial
19 and you don't really know the quality of what you did,
20 and the trial is negative and so an academician on a
21 cutting edge of a new technology sort of closes that
22 door off, that's a tragedy. And I think a lot of that
23 is even more of a tragedy in a field that up until now
24 has been struggling for its big successes in the last
25 several years. So I think again, there's just this

1 educational process is going to be critical for the
2 field in academia.
3 Any comments? I mean does anyone disagree
4 with that summary? Did I miss something important?
5 Okay, Carolyn, you're on. Talk about
6 retroviral vector production.
7 DR. WILSON: Good morning. I want to
8 first just begin by clarifying that what I'm talking
9 about today are retroviral vectors that are currently
10 used in clinical trials and these are vectors that are
11 derived from a class or group of retroviruses known
12 as, known now as gamma retroviruses. These vectors
13 have been engineered so that when they are produced
14 they are defective. They can no longer replicate in
15 their target cells and this is an important safety
16 feature.
17 However, there are occasions when there
18 can be what are called recombinational events that
19 occur during manufacture of these vectors where
20 replication properties are regained by these vectors.
21 And those are termed replication competent
22 retroviruses or RCR. And we consider these
23 contaminants and on the next slide the Agency's point
24 of view is that these are not only contaminants, but
25 also pose a safety concern and a risk to subjects in

1 these types of clinical trials.

2 To underscore this, I just wanted to
3 briefly remind people of a study that was done early
4 on by Robert Donohue and his co-workers at Art
5 Neidenai's lab where -- this actually wasn't a
6 serendipitous finding where they were doing some
7 preclinical studies for an ex vivo gene therapy using
8 bone marrow transduction and it turns out that their
9 preparation of retroviral vector was heavily
10 contaminated with RCR. And when these immune
11 suppressed monkeys received the bone marrow
12 transplant, within 200 days, three out of 10 developed
13 lymphomas and died.

14 Subsequent molecular analyses of tumor
15 tissue from these animals demonstrated that there were
16 sequences present in that tissue that were
17 recombinants between the vector and helper sequences
18 from the vector producer cells or vector and cellular
19 sequences.

20 Next slide, please. Because of the
21 recognized concern of presence of RCR actually over a
22 number of years, the Agency has been developing
23 guidance in this area and as early as 1993, developed
24 more stringent guidance about how to test these types
25 of products for presence of RCR during manufacture.

1 The most recent guidance was issued in October 2000.
2 I'm not going to go into that in any detail. It's
3 available on the web and the title is shown here, but
4 I just wanted to briefly say we do give detailed
5 recommendations about how to do RCR testing at
6 multiple points during manufacture, but we also still
7 ask for a follow-up of patients in these clinical
8 trials.
9 Next slide, please. In the March 6th
10 letter, as Joyce mentioned this morning, the fourth
11 question asked for information about lots that were
12 rejected for clinical use and the reasons for why it
13 was rejected. We viewed this as an opportunity to
14 gain some information about what types of vector
15 producer cells had reported incidents of RCR detection
16 during manufacture. Again, as Joyce also mentioned,
17 I wanted to just point out this represents only those
18 currently active files. So the files that are no
19 longer treating patients did not provide a response to
20 the March 6th letter. So it's meant to really
21 represent trends and only in the currently active
22 files.
23 Before I go on with that data, what I want
24 to briefly do just so you have an appreciation of what
25 these different vector producer cells are about is to

1 just quickly go through the technology and how some of
2 the vector producer cells have been designed to try to
3 reduce incidents of RCR.
4 Next slide, please. Essentially, the
5 gamma retrovirus, these are simple retroviruses
6 compared to the virus that you probably most know
7 about, Human Immunodeficiency Virus. It has only has
8 three open reading frames called Gag, Pol and Envelope
9 and then it has LTR or Long Terminal Repeats at either
10 end and this size sequence is a packaging sequence
11 which allows for a viral RNA to be packaged in the
12 particle.
13 In the design of retroviral vectors, you
14 can typically think of this genome or actually this is
15 a provirus structure being divided into what are
16 called retroviral helper sequences which encode the
17 transacting elements for production which have the
18 coding sequences, Gag, Pol and Env and the vector
19 sequences which contain the cyst acting elements that
20 are required for packaging, reverse transcription
21 integration and transcription.
22 On the next slide this a sort of cartoon
23 of what a typical vector producer cell might look
24 like. The helper sequences and the vector sequences
25 have been introduced on plasmids and then become

1 integrated into the genome of a mammalian cell and the
2 RNA is expressed. In the case of the helper
3 sequences, these are translated into viral proteins.
4 Because this RNA does not contain the packaging
5 element, that RNA isn't packaged into the vector
6 particle, but rather the helper, I mean the vector
7 sequence that does contain the psi element will be in
8 the vector.

9 So these elements come together at the
10 surface of the plasma membrane, but through and you
11 get a vector particle. These particles are
12 structurally identical to a retrovirus, a wild type
13 retrovirus, but they no longer contain the coding
14 sequences to make progeny variants.

15 In a stoicastic manner, there are
16 occasions where you get recombinational events between
17 these sequences or in the case of, for example, murine
18 cell lines that have their own endogenous retrovirus
19 sequences that have homology to these elements, those
20 can also participate in recombination and generation
21 of a wild type viral RNA which can then be packaged
22 and then we have an RCR.

23 Next slide, please. Over the course of
24 really the last 15 years, scientists have been working
25 on designing vector producer cells which have reduced

1 incidences of RCE for obvious reasons and some of the
2 strategies that have been applied are to eliminate
3 sequences of homology so that there's less opportunity
4 for recombination, so overlapping sequences between
5 vector and helper, using cells that don't have
6 homologous endogenous retroviruses, splitting up the
7 helper sequences into more than cassette, for example,
8 Gag-Pol is typically separated from the envelope. And
9 introduction of stop codons in any of the open reading
10 frames that might still be present on the vector
11 sequences, for example, the Gag overlaps with the
12 packaging element, so you usually have a little bit of
13 Gag on the vector sequence.
14 Next slide, please. So now I just wanted
15 to very quickly go through this summary table and I
16 know this is going to be hard for people in the back
17 to see and I apologize, but I wanted to be able to
18 capture for each vector producer cell that's being
19 used in clinical trials, that critical information as
20 it may correlate with the detection of RCR during
21 manufacture. So I've listed whether or not it's a
22 murine or human cell line, how the helper sequences
23 are designed, the envelope, and what we observed in
24 response to Question 4 in terms of reports of RCR
25 detection.

1 PA317, notably, is the only vector
2 producer cell still being used for clinical trials
3 that has only a single expression cassette for the
4 helper sequences. And we've observed that it was
5 fairly common that manufacturers who were using this
6 packaging cell line have lots that are positive for
7 RCR.
8 Two -- what you might consider second
9 generation cell lines that have two expression
10 cassettes, but are still in a murine cell background
11 also had reported lots that were positive for RCR, but
12 at a lower frequency.
13 PG13 which is still a murine, two
14 expression cassettes, but now has a more heterologous
15 envelope given a leukemia virus with reduced homology
16 to the endogenous murine retroviruses so far has not
17 had any reports of RCR and this other category
18 actually represents several different producer systems
19 that are used in a human cell line, also two
20 expression cassettes and the amphotropic envelope in
21 this case and so far, again, no reports of RCR
22 positive lots.
23 I just wanted to mention these last two,
24 in particular, have been used -- their implementation
25 for production of vectors in clinical trials is more

1 recent and so our cumulative experience with these is
2 somewhat less. So this may not be an absolute no as
3 time goes on.
4 Next slide, please. I wanted to just give
5 you also a snapshot from one production laboratories.
6 This is actually a National Gene Vector Lab at Indiana
7 University. This data was kindly provided by Ken
8 Cornette and Lilith Reeves. The provided to the FDA
9 their total summary of all their production lots for
10 clinical trials with the different vector producer
11 cells. And consistent with what we saw in the
12 response to the March 6th letter in general, they see
13 really a fairly high incidence of RCR positive lots
14 when they used PA317. This is reduced with AM-12 and
15 although this is only an N of 2 for Psi-CRIP, so far
16 they haven't had any RCR positive lots. PG13 for 14
17 lots produced is still, so far have not produced any
18 RCE positive lots.
19 Next slide. What I just want to finish
20 with is first of all, I think we need to recognize
21 that there are some assurances here that, in fact, in
22 the later generation of vector producer cells, what
23 we're seeing is that design elements that were meant
24 to reduce incidents of RCR during actual manufacture
25 for clinical lots is resulting in a reduced incidence

1 of RCR and I think that's the good news. And I also
2 just wanted to sort of put a plug in, not only is
3 training and outreach from our perspective important,
4 but it's equally important for us to be able to
5 continue to have these kind of dialogues and the
6 public and for investigators to continue to try to get
7 as much of their data out into the public domain on
8 these issues as well.
9 And so with that, I'll just turn to the
10 next slide which has the question for discussion for
11 the Committee. Thank you for your attention.
12 Do you want me to read the question or do
13 you want to read it?
14 DR. SALOMON: I can probably read it.
15 Thank you, Carolyn. The -- I'm trying to think of the
16 best way to do this. I think what I'd like to do is
17 take a break now. I think we've been sitting here for
18 a while and come back and deal with these questions
19 and the subsequent presentations, if that's okay with
20 everybody.
21 So ten minutes, and be back here at 11.
22 Thank you.
23 (Off the record.)
24 DR. SALOMON: If we can get everybody back
25 to their seats so we can start again after the break.

1 As everybody knows whenever Jay sits down, that's my
2 official signal. Jay is good. I might have to pick
3 someone else like Phil, because you've gotten real
4 good about it.
5 Okay, if we can get the audience to sit
6 down as well. I need a gavel. Can we have like maybe
7 a sudden loud feedback?
8 (Laughter.)
9 Okay, thank you, everybody. I'd like to
10 first introduce on new Member to the Panel.
11 Dr. Roessler, can you just give us a quick
12 brief on who you are and what your expertise is?
13 DR. ROESSLER: I'm Blake Roessler at the
14 University of Michigan and at the National Gene Vector
15 Laboratory and our center has been manufacturing
16 plasma DNA for use in clinical trials.
17 DR. SALOMON: Thank you. Okay, well. So
18 the point where we're at now is after the presentation
19 of Carolyn Wilson on replication competent retrovirus
20 and retroviral packaging lines, she posed for us a
21 question that based on currently available data
22 regarding RCR detection during vector manufacture, and
23 she's referring now specifically to the table showing
24 the different vector packaging cells, the VPCs, is it
25 reasonable for CBER to disallow in the future in INDs,

1 the use of VPCs with a single expression cassette for
2 the helper sequences such as PA-317?
3 Any comments from the Committee? Richard?
4 DR. MULLIGAN: I think it's not exactly a
5 burning question is my opinion, but my answer would be
6 no. I think one thing that was listed on the
7 overhead, but not really appreciated is how key the
8 vector is to a packaging cell, that is, pairing the
9 right vector to the packaging cell is really the key
10 and you can take a lousy packing cell and use a good
11 vector in the packaging cell and tend to get no
12 difficulties, or you can use a very good packaging
13 cell that is constructed, designed in a proper fashion
14 with a lousy vector and have difficulties.
15 And so I think that you cannot in a
16 blanket fashion take a particular packaging cell and
17 say no. I think I would rough up anyone who would
18 suggest using PA-317 and really ask them why would you
19 possibly do that, but I think it's not actually worthy
20 of a lot of our time and effort. I would focus on
21 issues that have to do with the details of vector
22 design and how they influence things and also the
23 issue of how you introduce the vector to the packaging
24 cell. One thing that we've never really published,
25 but we've always had a sense of, is that doing

1 so-called ping-pong infection or cross infection to
2 make the packaging cells is not a good way to make
3 clinical grade packaging cells and there's some
4 technical reasons we don't really need to go into at
5 this point on why that may not be a good idea. But I
6 think there's some real reasons where I would -- I
7 think that's a far more significant question of
8 whether there's mutations associated with cross
9 infection. that means you have to test the product in
10 a different fashion. There's issues of whether or not
11 the use of cross infection simply improves, increases
12 the frequency of transmission of other endogenous
13 sequences. So I think those are more the kinds of
14 issues.
15 The last thing I'd mention is people over
16 the years have really not appreciated other things,
17 other transmission issues other than replication
18 competent and I think although it may not be that much
19 of an issue at this point with the Lentivectors, the
20 whole issue of whether or not these packaging systems
21 are predisposed to transmission of a portion of the
22 packaging sequences I think is very, very important
23 and I think that if you look at all the literature,
24 people really have not addressed. I think very
25 recently there's some people that have begun to look

1 at this, but I think that's going to be key, that is
2 the fact that even without any packaging sequences of
3 nonretroviral genomes can be packaged with some
4 frequency and depending with what else is co-packaged,
5 you can transmit those sequences. And so, I think
6 that those are the kinds of issues that are key. But
7 here, I would just leave it to the sense of the FDA
8 which I think is a consensus of the scientific
9 community that these single genome packaging cells are
10 just not the latest and the greatest. So why would
11 you use them?
12 DR. SALOMON: Carolyn, do you have a
13 comment on that?
14 DR. WILSON: I just wanted to make one
15 point for clarification which is that in production of
16 clinical grade retroviral vectors, we don't approve
17 INDs that use the ping-pong method of manufacture.
18 That's been the status for quite some time.
19 DR. SALOMON: So -- what I see here as an
20 interesting issue --
21 DR. MULLIGAN: Excuse me, just to clarify.
22 Even a single pass of virus? Because I think the same
23 holds to the single pass.
24 DR. WILSON: Okay, yes, we do allow for
25 the single pass. I thought you meant when they go

1 back and forth. And when they do, we do ask for
2 additional testing, for example, for the ecotropic RCR
3 that could be introduced from that method.
4 DR. MULLIGAN: Because even the single
5 pass predisposes you to things that couldn't happen by
6 the transvection. So you know, if you're unlucky,
7 very unlucky and some people are, you can actually get
8 a cross infection that will give you a point mutation,
9 even though it may be an error and if you happen to
10 pick that as your producing cell, then your product
11 has mutation in it and you're probably not or you
12 haven't in the past asked people to actually sequence
13 the proviral DNA. But that is a difficulty that you
14 wouldn't have, at least not the same extent by just
15 the transvection of the sequences.
16 DR. WILSON: That's correct, but as you
17 know, that's actually a topic that we discussed in
18 November and we're trying to evolve our policy in that
19 area as well, so that a master cell bank that you
20 would derive then would have sequencing of -- we were
21 thinking of the viral genomic RNA as a one-time basis
22 to qualify and make sure that just the type of thing
23 that you're suggesting wouldn't have occurred.
24 DR. SALOMON: Yes, Richard, you missed the
25 last one. I know you had to leave, but the final --

1 the second day. The final was any vector up to 40KB
2 had to be sequenced.
3 DR. MULLIGAN: Yes, well, I did miss it,
4 so I'm not sure what you said, but I thought when I
5 left that you had to sequence the parental DNA. But
6 the question is, what we're talking about here is the
7 actual if you were to do a viral infection and
8 generate the packaging cells, would you have to
9 actually sequence what had undergone reverse
10 transcription and become DNA from the input of RNA?
11 DR. WILSON: And that's where we're in the
12 process of evolving our policy recommendations on to
13 address that exact point.
14 DR. SALOMON: That was certainly the
15 spirit of it, at least my understanding of the spirit
16 of it. We knew what we were producing, not what we
17 thought we went into at some point.
18 DR. MULLIGAN: Right. The one last issue
19 with the helper is that although there's obviously
20 other events that are important for a retrovirus, a
21 non-oncogenic or a non-oncogene containing retrovirus
22 to cause a tumor, it's generally thought the simple
23 version is that it's the number of hits, the number of
24 integrations that are important and I used to make
25 this joke in the past, at these BRMAC meetings 10

1 years ago that all people have proven so far in gene
2 therapy is that if you don't have any gene transfer
3 occur, it's a perfectly safe approach.
4 (Laughter.)
5 And it's very important here because the
6 results that we have showing the tumors are presumably
7 the results of many more integrations of sequences and
8 people ought to be aware of the fact that as the
9 vectors get higher titer by thousand fold or so, and
10 we finally figure out how to transduce stem cells,
11 that you're going to have a risk not from replication
12 competent virus, but you're going to go back to the
13 risk that everyone never really wanted to talk about
14 which was if you load enough proviral copies, you're
15 going to hit a location that's not a good location.
16 And therefore, going back and trying to analyze those
17 earlier Neinheis results might be quite important from
18 the point of view of do we really have the sense of
19 just in the simple number of book integrations that
20 have occurred that led to this event, how far away are
21 we from an in vivo gene therapy with a vector that now
22 integrates into resting cells at high efficiency.
23 Could we actually get the same number of events and
24 would we then be concerned about that?
25 DR. WILSON: To address that point,

1 actually, I believe it's the Purcell paper that I
2 cited, does show, if I recall correctly, around 20 to
3 30 copy numbers in the tumor tissue, so your point is
4 well taken, that it certainly does take multiple hits.
5 And I also just to focus on that point, that's the
6 reason why even in our patient follow-up, when we look
7 for evidence of RCR infection and it's even negative
8 at one year, we continue to recommend follow-up of
9 patients past that point for the very reason you're
10 suggesting, that the vector per se can also have the
11 potential to integrate into a cite that could have
12 potential tumorigenic consequences. And that will
13 also be a topic we'll be discussing more tomorrow.
14 DR. SALOMON: Yes. I want to say that
15 these are really important discussions, that's why I
16 didn't cut them off, but we want to talk right now
17 about production issue and the questions we're not
18 segueing into are critical, but they're more what's
19 going to happen after you institute the trial and we
20 should get back to those.
21 I guess the comment that I had, just to
22 make sure that we have a little bit of discussion
23 before -- I always like the basic principle of not
24 just making a policy that then creates a rule that
25 might later reduce some flexibility that a reasonable

1 scientist, based on very rational sets of thinking
2 suddenly wants to use this vector, for example,
3 PA-317. On the other hand, I think there is a safety
4 issue that's overarching this. When you have, I
5 guess, data where 75 percent of the production lots
6 had RCR contaminating them, and you concerned yourself
7 with the idea that any sort of testing strategy might
8 miss that once in a while, is it really safe? Should
9 we not just ban single help, single package, single
10 cassette, expression cassette lines like this when
11 they have such a bad record?
12 DR. MULLIGAN: I haven't really looked at
13 the data enough to look at vectors that are used with
14 the packaging cells, but I think you'd have to do a
15 very careful analysis, a very detailed analysis of
16 what vector was used in a case where this did happen,
17 what were the circumstances in terms of how they did
18 the transvection, how they picked the things. The
19 other issue that probably is not pertinent here is how
20 often are they actually false positives? How often
21 can you repeat the positivity? Again, I could go
22 either way on this, but I don't think it's a real big
23 enough issue to set a precedent because that means
24 that then as other things come down the pike, I mean
25 this is such a no brainer in a way that this is okay

1 if you want to set the policy on this, but things are
2 not going to be no brainers in the future. There's
3 going to be something that's a little better than
4 PA-317, but still not very good and then you're going
5 to have to say now where do I make the cut and who's
6 going to make that cut? I think everyone probably
7 agrees that this is a nefarious cell relative to other
8 things and I don't know of any single biological
9 property of those cells that would make someone say
10 well, we got to use those because they do something.
11 DR. SALOMON: Exactly. That was my point.
12 On the other hand, I hear what you're saying, that --
13 I guess that's always the thing that we're monitoring,
14 right? At what point are we in development of a field
15 where we don't need necessarily to make a complicated
16 decision, yes, you can't have a single expression. I
17 guess that's probably not correct and maybe what we
18 ought to do is leave it as I think there's general
19 agreement here that you don't want to see replication
20 competent retrovirus. I think the other thing that
21 the data shows is that this kind of data actually will
22 continue to grow and be available in the sense that
23 the percentage of replication competent retrovirus
24 contaminating lots will come out and that should be a
25 gauge. You should have to show that kind of data.

1 Moreover, I guess it would be something
2 that would raise an appropriate alarm if I came up to
3 you and said I've got a new trial and I've got a new
4 packaging line that has no history at all and then
5 questions like what kind of vectors do you put in,
6 maybe there ought to be some data where you put in
7 four or five different kinds of vectors and show that
8 you're not getting RCRs. I mean maybe the general
9 principles are on the ground and we don't need to do
10 anything more. I think that's what I'm hearing here.
11 DR. MULLIGAN: I just thought of one case
12 in point that someone might make for the PA-317 which
13 is that a company might say look, optimize the large
14 scale production of these cells for five years and
15 this is unique and every cell is different and that's
16 why we want to use these and I think that's somewhat
17 of an argument, so I think there are going to be
18 compelling reasons, but I think it's perfectly
19 reasonable to discourage the use of it and try to
20 probe why it's necessary and you know, -- that's all.
21 DR. NOGUCHI: If I could comment, I think
22 we appreciate the need to be flexible as much as
23 possible, but the other way to look at it is we're
24 asking for a scientific evaluation of what data that
25 we have and in the context of the larger picture that

1 all these things are complicated. We have not had any
2 true demonstrated, long-term success as yet. Maybe
3 some encouraging results.
4 Would you, as part of this Committee
5 advising us, do you really think that it's, as you
6 correctly point out, there are many larger issues,
7 does that mean then that we can't put this one to rest
8 so we always have to have open the ability for
9 somebody to come in and say well, look, I want to use
10 this for the following reasons. We have to evaluate
11 that. We have to figure out what kind of designs or
12 tests we're going to say to make sure that, in fact,
13 the reasons for using this outweigh the risks that it
14 might occur?
15 Partly, the question we're asking is a
16 simple one, but it is an important one. Are there
17 some things that just aren't worth pursuing? That's
18 the question.
19 DR. MULLIGAN: I think that I just don't
20 personally have enough of the scientific information
21 to fully evaluate the properties, the total properties
22 of packaging cells and vector, so I'm just saying you
23 may have that, but I wouldn't be convinced until I
24 went and looked at that information. For instance, it
25 may be that there are certain kinds of vectors that

1 are generally used because someone develops the vector
2 and someone develops the packaging cell, so it might
3 be that typically you use a certain type of vector
4 with PA-317, just because you get sent a vector and
5 you get the packing cells in the same person. And it
6 may be, it may tell you something. It may tell you
7 that using this vector leads to this difficulty, but
8 another vector doesn't lead to it. So I don't think
9 there's enough, but before I as an expert could
10 actually commit to saying you ought to derive a stake
11 in the heart of this packaging cell, I would want to
12 see much more detailed scientific information about
13 the properties and what happened.
14 DR. NOGUCHI: At the cost of more clinical
15 trials?
16 DR. MULLIGAN: Oh no.
17 DR. NOGUCHI: No, I mean with -- using
18 this vector or this packaging cell line with at least
19 some potential for being less efficient in producing
20 a clinically acceptable vector. That's part of the
21 equation here.
22 If we could be assured that in fact,
23 scientists would be looking and stressing the system
24 in experiments not designed for clinical trials, that
25 would be one way to approach it, but that's not what's

1 being done. What is being done is these are being
2 used at very high titers, or relatively high titers,
3 specifically because that's the amount that is needed
4 for a clinical trial.
5 We're pushing you and asking, do you think
6 it's worth doing any more clinical trials or some more
7 or how many more clinical trials with a product where
8 we know a goodly proportion of the vectors that are
9 produced will not be acceptable, that's an additional
10 cost that does leave the potential risk because the
11 limits of detection may not be appropriate or always
12 the same?
13 That's the real question. We're asking a
14 very hard question between the starkness of scientific
15 discovery and pushing the envelope and finding out as
16 much as we can versus a very real concern that to
17 progress, we need better vectors. Is this the best
18 way to do that? And is it worth the human
19 experimentation that is going to drive the production
20 of these vectors?
21 DR. MULLIGAN: I remember this argument
22 over a decade ago with the evolution of the first
23 Psi-2 cells and so forth and I remember distinctly the
24 consensus point of view being this is all theoretical.
25 Because I remember when we developed the first of

1 these split packaging cells and we were mentioning the
2 importance of the theoretical safety advantages, I
3 remember many people said well, gee, isn't this really
4 theoretical? The test is the test. If you do the
5 test and it comes out clean, then you use the stuff.
6 You could argue from, I think, the line that you're
7 taking, if you ever saw with any packaging cell, a
8 batch that had replication competent virus, you might
9 think that there's something deficient with that cell
10 and you might then be concerned about using that in
11 the future. I mean the argument is not that
12 different, if you ever find something happening. I
13 suppose it's the case that if you had something that
14 you never saw any helper virus, you might think that
15 that meets the absolute test, but as you know, as the
16 tests get more sensitive, you begin to pick up things
17 you didn't pick up before.
18 DR. NOGUCHI: Yes, but this is not a
19 single case. This is multiple cases. This is 10
20 years of experience.
21 Are you saying that we cannot use our
22 experience to exclude things?
23 DR. MULLIGAN: Well, I would feel more
24 comfortable, I cannot say here that I would want to
25 get rid of it without seeing what the data is. I

1 think you owe it to everyone to -- well, I mean you
2 have to tell us how much investigation you had of the
3 actual vector and the method of generating the
4 packaging cells, because I think that that's
5 important. Because what you might be doing is
6 revealing something that's not PA-317 specific and if
7 that's the case you want to know that. That is, your
8 assumption is that if something because it's a single
9 gene, but it may not be, and you would hate to miss
10 that if turned out it was the way you did -- the way
11 people generally did those transvections, the way they
12 cultured the cells or some other property. So I think
13 there's incomplete information.
14 I'd be happy, if you want, to review that
15 information, but I would not be comfortable saying
16 that you shouldn't use this.
17 All that being said, I'm sorry, we spent
18 so much time on it. I mean I actually think it's --
19 I wouldn't feel awful if you rammed it, I just think
20 it's something -- clearly there's better things.
21 There's no question about that. But in this field, as
22 you know, there's always better things. And I think
23 it begins to get complicated once you try to figure
24 out what's better and how much better does the next
25 thing have to be before you can the first thing.

1 DR. SALOMON: Dr. O'Fallon?

2 DR. O'FALLON: Yes, I was just going to
3 point out that the data that you brought to us is
4 summarized in Tables 1 and 2 of our previous
5 presentation and it says yes, fairly common. That's
6 not a very good quantifiable concept and in the next
7 table there's three out of four, also not very
8 impressive from a statistical standpoint.

9 We might start on a slippery slope, but if
10 this Committee makes judgments on such small lot of
11 data that we certainly wouldn't make the same judgment
12 and approve a product if somebody said we would have
13 3 out of 4 successes on a clinical trial.

14 DR. SIEGEL: If you had 3 out of 4
15 fatalities though you might make a judgment that it
16 was unsafe.

17 DR. SALOMON: Right.

18 DR. O'FALLON: I agree.

19 DR. SALOMON: Dr. Chanock.

20 DR. CHANOCK: I was going to say on the
21 last point, I agree fully about the question of the
22 statistical nature, but the other issue to come back
23 to the question is are we sure that we can blame it on
24 the PA-137s per se and not some methodologic question?
25 And I think that with this amount of data I wouldn't

1 want to throw the baby out with the bath water, so to
2 speak if there are opportunities for people who are
3 still trying to develop and improve the vector
4 technology to be able to use that and I think that you
5 are going to find that if there's a set of
6 restrictions or a set of guidelines set down for RCRs,
7 then those are going to help to drive the choice on
8 the part of the individual investigators into
9 commercial outfits, so I think it will partly drive
10 itself, so I would be worried about cutting it off at
11 the pass right now, unless there was more information
12 that would be more compelling, at least that is
13 forthcoming.

14 DR. SALOMON: I think to just in the
15 interest of moving on, I think what I hear from
16 everyone and I certainly agree as well, is that the
17 Committee is willing to consider the possibility that
18 a cell line with a bad enough track record might be
19 taken off the market unless someone -- it wouldn't
20 stop anyone from coming back later and saying look, if
21 I do this and this, it's wonderful. You should take
22 that for merit. I think that what you're hearing is
23 is that we ought to set a series of guidelines for the
24 use and selection of these vectors. To pick up
25 something that was emphasized in the last meeting in