UNITED STATES OF AMERICA

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

PUBLIC HEALTH SERVICE

FOOD AND DRUG ADMINISTRATION

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CENTER FOR BIOLOGICS EVALUATION & RESEARCH

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VACCINES AND RELATED BIOLOGICAL PRODUCTS
ADVISORY COMMITTEE MEETING

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THURSDAY
NOVEMBER 19, 1998

The meeting took place in the Versailles Rooms I and II, Holiday Inn, Bethesda, Maryland, at 8:00 a.m., Patricia L. Ferrieri, M.D., Chair, presiding.

PRESENT:

| | |
|---|---|
| PATRICIA L. FERRIERI, M.D. | Chair |
| NANCY CHERRY | Executive Secretary |
| ADAORA A. ADIMORA, M.D. | Member |
| REBECCA E. COLE | Member |
| ROBERT S. DAUM, M.D. | Member |
| KATHRYN M. EDWARDS, M.D. | Member |
| DIANNE M. FINKELSTEIN, Ph.D. | Member |
| HARRY B. GREENBERG, M.D. | Member |
| CAROLINE B. HALL, M.D. | Member |
| ALICE S. HUANG, Ph.D. | Member |
| KWANG SIK KIM, M.D. | Member |
| STEVE KOHL, M.D. | Member |
| GREGORY A. POLAND, M.D. | Member |
| DIXIE E. SNIDER, Jr., M.D., MPH | Member |

OPEN

INVITED PARTICIPANTS:

DON BLAIR, Ph.D.
ROBERT BREIMAN, M.D.
THEODORE EICKHOFF, M.D.
THOMAS FOLKS, M.D.
STEPHEN HUGHES, Ph.D.
MARGARET JOHNSTON, Ph.D.
NEAL NATHANSON, M.D.
MICHAEL OXMAN, M.D.
GEOFFREY SCHILD, Ph.D.
WILLIAM WOLD, Ph.D.
SIDNEY WOLFE, M.D.

SPEAKERS:

DR. LESLIE BALL
DR. NORMAL BAYLOR
DR. KATHLEEN CLOUSE
DR. KAREN ELKINS
DR. LYDIA FALK
DR. CARL FRASCH
DR. ANTONIA GEBER
DR. ARIFA KHAN
DR. PHILIP KRAUSE
DR. ROLAND LEVENDOWSKI
DR. ANDY LEWIS
DR. DOUGLAS PRATT
DR. BECKY SHEETS

ALSO PRESENT:

CAROLYN HARDEGREE, M.D.

# A G E N D A

Page

Call to order, Announcements and Administrative Matters, Introductions . . . . . . . . 4

Tribute to Dr. Mary Lou Clements-Mann . . . . . . . 9

**Open Public Hearing**

Update on Approved Products . . . . . . . . . . 12
**Dr. Norman Baylor**

Update on reverse transcriptase activity in chicken cell derived vaccines . . . . . . . 13
**Dr. Arifa Khan**

The evolving use of animal cells as vaccine substrates . . . . . 29
**Dr. Andy Lewis**

Evolving cell substrate issues as they pertain to investigational vaccines . . 63
**Dr. Becky Sheets**

Experience with therapeutics derived from mammalian cells . . . 92
**Dr. Kathleen Clouse**

Studies on safety of cell lines . . . . . . 112
**Dr. Philip Krause**

Items for the Committee to discuss . . . 141
**Dr. Andy Lewis**

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

2 (8:10 a.m.)

3 CHAIRPERSON FERRIERI: I'd like to call

4 the meeting to order.

5 If you could all take your seats. Those

6 of you who are sitting up here at the table, if you

7 could find your seats, please. And this is an open

8 session, and so we don't have to validate anyone at

9 this time.

10 I'd like to start by introducing myself,

11 Patricia Ferrieri, from the University of Minnesota

12 Medical School, Departments of Lab Medicine and

13 Pathology and Pediatrics. And I'm the Chair of the

14 Committee, and I'd like to have introductions of

15 everyone at the table.

16 If you could state your names and your

17 institution, we'll start at my far right and work

18 around.

19 Dr. Greenberg.

20 DR. GREENBERG: Harry Greenberg, Stanford

21 University in the Palo Alto VA Hospital.

22 DR. EDWARDS: Kathy Edwards, Vanderbilt

23 University, Nashville, Tennessee.

24 DR. SNIDER: Dixie Snider, Centers for

25 Disease Control and Prevention.

1 DR. POLAND: Greg Poland, Mayo Clinic,
2 Rochester.
3 DR. KIM: Kwang Sik Kim, Children's
4 Hospital, Los Angeles.
5 DR. HALL: Caroline Hall, University of
6 Rochester, New York.
7 DR. KOHL: Steve Kohl, University of
8 California, San Francisco.
9 MS. COLE: Rebecca Cole, Consumer
10 Representative from Chapel Hill, North Carolina.
11 DR. DAUM: I'm Robert Daum from the
12 University of Chicago.
13 MS. CHERRY: Nancy Cherry, FDA.
14 DR. BREIMAN: Rob Breiman, National
15 Vaccine Program Office.
16 DR. NATHANSON: I'm Neal Nathanson from
17 the Office of AIDS Research.
18 DR. EICKHOFF: Ted Eickhoff, University of
19 Colorado.
20 DR. OXMAN: Mike Oxman, the University of
21 California, San Diego, and the VA Medical Center in
22 San Diego.
23 DR. FOLKS: Tom Folks, Center For Disease
24 Control and Prevention.
25 DR. WOLFE: Sid Wolfe, Public Citizens

1 Health Research Group.

2 DR. WOLD: Bill Wold, St. Louis

3 University.

4 DR. BLAIR: Don Blair, NCI, Frederick.

5 DR. JOHNSTON: Peggy Johnston, NIAID.

6 DR. HUGHES: Steve Hughes, ABL BRP at the

7 Frederick Cancer Research and Development Center.

8 CHAIRPERSON FERRIERI: Thank you very

9 much.

10 Some of the members are missing, and we'll

11 introduce them as they join us.

12 I'd like now to turn the meeting over to

13 Ms. Cherry for various administrative matters.

14 MS. CHERRY: Well, I, of course, have the

15 conflict of interest statement, or the meeting

16 statement, to read into the record.

17 This announcement is read into the record

18 at this meeting of the Vaccines and Related Biological

19 Products Advisory Committee on November 19 and 20,

20 1998. For this meeting, FDA has invited a number of

21 consultants and guests to participate in the meeting.

22 The Agency has determined that the

23 services of the guests are essential to the committee

24 discussions. No temporary voting privileges have been

25 extended at this meeting.

1 Dr. Broome, although listed on your roster
2 of participants, was unable to be with us today.
3 Screenings were conducted to prevent any
4 appearance, real or apparent, of conflict of interest
5 in the meeting discussions here at this meeting.
6 Based on the agenda made available and on
7 relevant data reported by participating members and
8 consultants, it has been determined that all financial
9 interests and firms regulated by CBER that could be
10 affected by the Committee's discussions have been
11 considered.
12 In accordance with 18 USC 208, some
13 members and consultants required and have been granted
14 general matters waivers. These waivers permit Drs.
15 Edwards, Greenberg, Hall, Huang, Hughes, Kilbourne,
16 Kohl, Murphy, Poland and Wright to participate fully
17 in all Committee discussions.
18 Dr. Daum has been granted a waiver
19 permitting him to participate fully in the Committee
20 discussions on cell substrate issues.
21 The following reported interests are being
22 made public to allow meeting participants to evaluate
23 objectively any presentation and/or comments made by
24 guests seated at our table:
25 For the session on cell substrate issues,

1 Dr. Donald Blair is employed by NCI; Dr. William Wold
2 reported grants with NCI and collaboration with
3 Immunex; and Dr. Michael Oxman reported collaboration
4 with Merck and the VA Cooperative Studies Program,
5 research grants from Merck Consulting supported by
6 Merck and SmithKline Beecham, and possible future
7 collaboration with Dr. Ann Arvin.
8 For the session on live influenza virus
9 vaccines, Dr. Robert Chanock is employed by NIAID in
10 the Laboratory of Infectious Diseases.
11 Copies of all waivers and appearance
12 documents addressed in this announcement are available
13 by written request under the Freedom of Information
14 Act.
15 In the event that the discussions involve
16 specific products or pharms not on the agenda for
17 which FDA's participants have a financial interest,
18 the participants are aware of the need to exclude
19 themselves from such involvement, and their exclusion
20 will be noted for the record.
21 With respect to all other meeting
22 participants, we ask, in the interest of fairness,
23 that you address any current or previous financial
24 involvement with any firm whose products you wish to
25 comment on.

1 That's it.

2 CHAIRPERSON FERRIERI: Thank you, Nancy.

3 I would like to pay tribute to Dr. Mary

4 Lou Clements-Mann, who was a member of our Committee.

5 And this is on behalf of the other Committee members,

6 as well as FDA.

7 Mary Lou and her husband, Jonathan Mann,

8 died on September 2nd on Swiss Air flight 111 when it

9 crashed off the coast of Nova Scotia. She was on her

10 way to an AIDS meeting at WHO in Switzerland. Mary

11 Lou made many contributions to our Committee.

12 We enjoyed particularly her incisive

13 judgement, her analyses, her thoughtfulness, and the

14 twinkle in her eye when she spoke.

15 She was Professor at Johns Hopkins

16 University in the Department of International Health

17 in the School of Hygiene and Public Health and was

18 known for her vast efforts in the field of vaccines,

19 had contributed greatly to studies of diarrhea and

20 respiratory pathogens, and was, in more recent years,

21 actively involved in AIDS vaccine development and

22 implementation.

23 I would like to dedicate a poem to her by

24 the late Polish poet Wislawa Szymborska, the 1996

25 Nobel Laureate for Literature. And this poem is from

1 a volume *View With a Grain of Sand.* It's titled
2 "Nothing's a Gift."
3 "Nothing's a gift, it's all on loan.
4 I'm drowning in debts up to my ears.
5 I'll have to pay for myself
6 with myself,
7 give up my life for my life.
8 Here's how it's arranged:
9 The heart can be repossessed,
10 the liver, too,
11 and each single finger and toe.
12 Too late to tear up the terms,
13 my debts will be repaid,
14 and I'll be fleeced,
15 Or, more precisely, flayed.
16 I move about the planet
17 In a crush of other debtors.
18 Some are saddled with the burden
19 of paying off their wings.
20 Others must, willy-nilly,
21 account for every leaf.
22 Every tissue in us lies
23 on the debit side,
24 Not a tentacle or tendril
25 is for keeps.

1 The inventory, infinitely detailed,
2 implies we'll be left
3 not just empty-handed
4 but handless too.
5 I can't remember
6 where, when, and why
7 I let someone open
8 this account in my name.
9 We call the protest against this
10 the soul.
11 And it's the only item
12 not included on the list."
13 I'd like everyone to stand for a moment of
14 silent prayer or kind thoughts for the memory of Mary
15 Lou and Jonathan.
16 (Whereupon, a moment of silence was
17 observed.)
18 CHAIRPERSON FERRIERI: Thank you. Please
19 be seated.
20 We'll move now to the open public hearing.
21 Ms. Cherry will take over for this.
22 MS. CHERRY: At this time, we have
23 opportunity for anyone who wishes to make a statement.
24 There is a microphone in the center here.
25 No one had contacted me in advance, and I

1 see no one coming forward, so I will declare the open
2 public hearing closed at this time.
3 CHAIRPERSON FERRIERI: Thank you, Nancy.
4 We'll move then to Session I, an open
5 session on approved products, and we'll have an update
6 from Dr. Norman Baylor from FDA.
7 Dr. Baylor, will you step forward?
8 DR. BAYLOR: Good morning.
9 I wanted to briefly go over a couple of
10 approvals that we had since our last meeting. The
11 first one is an acellular pertussis vaccine absorbed,
12 and the trade name for this product is Certiva. It
13 was approved on July 29th of this year.
14 And it's a vaccine for the first four
15 doses in the series for DTaP. It's for the
16 immunization of infants and children six weeks of age
17 to seven years of age, prior to the seventh birthday.
18 This vaccine is manufactured by North
19 American Vaccine, Inc. in Beltsville, Maryland. And
20 the D&T components of this vaccine are manufactured by
21 Statens Serum Institute in Copenhagen, Denmark.
22 The other product license application that
23 we approved since the last meeting is for the
24 rotavirus vaccine. This is a live, oral, tetravalent
25 vaccine. The trade name of this vaccine is

1 RotaShield, and it was approved at the end of August
2 of this year.
3 And it's for the immunization of infants
4 two, four and six months of age. The first dose can
5 be given as early as six weeks of age, but the
6 initiation after the six months of age is currently
7 not recommended in the package insert.
8 This vaccine is manufactured by Wyeth
9 Lederle Laboratories, Inc. of Marietta, Pennsylvania.
10 We also had -- I don't have a slide for
11 it, but we had one major approval of a supplement for
12 the reissuance of a license for BCG vaccine
13 manufactured by Connaught Laboratories, Ltd. in
14 Toronto, Canada.
15 And that's all I have for you.
16 CHAIRPERSON FERRIERI: Thank you, Dr.
17 Baylor.
18 We'll now move into our longer session for
19 the morning -- it's also open -- on cell lines for
20 viral vaccines. And we'll begin with the update on
21 reverse transcriptase activity in chicken cell derived
22 vaccines presented by Dr. Arifa Khan from FDA.
23 DR. KHAN: Good morning.
24 Today I would like to present an update on
25 the reverse transcriptase activity that's present in

1 chicken cell derived vaccines.

2 I would like to present some of the
3 studies related to this topic that were presented to
4 the WHO earlier this year in April, as well as some
5 additional studies done in my lab related to -- that
6 addresses some theoretical concerns that remained with
7 regards to the presence of the RT activity in the
8 vaccines.

9 In the first slide I would just like to
10 give a brief background related to the chicken RT
11 activity and with regard -- and I've also indicated
12 publications up to date with regards to what has been
13 done on this issue.

14 Initially Böni, et al., in 1996, published
15 that low level reverse transcriptase activity was
16 detected in all chicken cell derived vaccines using a
17 highly sensitive PCR-based reverse transcriptase assay
18 called PERT, which can detect one to ten virions.

19 This initial finding was reported to the
20 WHO, and then additional studies were done by several
21 laboratories in Europe, as well as the U.S., including
22 the NIBSC, the CDC, as well as labs in the FDA to
23 confirm this initial finding, as well as to expand on
24 this and to evaluate the use of the PERT assay and
25 other PBRT-related assays for analysis of vaccines.

1 And these studies have been done and
2 published by Robertson, et al. in 1997 and by Dr.
3 Peden's lab by Maudru, et al. in 1998.
4 And after confirmation that there was a
5 reverse transcriptase activity present in all chicken
6 cell derived vaccines, the important question, of
7 course, was whether this RT activity was associated
8 with a retroviral particle; and, more importantly,
9 whether this retrovirus particle could infect and
10 replicate in human cells, and therefore be of public
11 health concern.
12 Studies done by other groups are
13 summarized here. The RT activity was found to be
14 associated with retroviral particles of two distinct
15 avian endogenous retroviral families designated as EAV
16 and ALV.
17 In addition, studies done in Dr.
18 Robertson's lab at the NIBSC and in my lab, in the
19 FDA, demonstrated that the RT activity originated from
20 the chicken cell substrate and that no replication
21 competent retrovirus was found using a variety of
22 different human cell lines including human PBMCs.
23 And interestingly, I've indicated in the
24 last bullet that, about 20 years ago, similar RT
25 activity was reported using the traditional assays

1 available at that time which was produced from CF
2 cultures and that was particle associated and
3 replication defective for chicken cells that were
4 tested at that time.
5 These studies, as well as other
6 information, were reviewed by the WHO early this year,
7 and they, as well as the FDA, continued use --
8 recommended continued use of the vaccines made in
9 chicken cells, and this report is published in July of
10 '98.
11 Okay, because there were retroviral
12 particles associated with the RT activity, there was
13 still a theoretical possibility that the virus could
14 enter the cell and infect the cell and the sequences
15 integrate into the human DNA.
16 The concern was because, for retroviruses,
17 there are examples in which retroviral-induced
18 oncogenesis can occur by insertional mutagenesis. And
19 I've listed some examples here in which case some
20 retroviruses can activate protooncogenes and, in more
21 rare cases, inactivation of tumor suppressor gene can
22 occur.
23 So to address this theoretical concern, my
24 lab initiated studies, in collaboration with Dr.
25 Shahabidene in my lab, to look at the infection and

1 integration of EAV-related sequences using human
2 PBMCs.
3 The next two slides indicates the strategy
4 that we used. There were two sources of material that
5 we analyzed.
6 We analyzed the chicken embryo fibroblast
7 supernatant, which we found to contain high levels of
8 the RT activity; as well as we used a control
9 production lot of the measles vaccine that was
10 equivalent to the vaccine that we indicate as MVE, or
11 measles vaccine equivalent.
12 In terms of the CF supernatant, what we're
13 looking at are the native retroviral particles that
14 will be produced from the cell substrate, as well as
15 contaminating DNA that's produced from the primary
16 culture due to cell lyses.
17 And this cellular DNA also contains
18 endogenous retroviral sequences, which are a normal
19 component of the host DNA.
20 In terms of the MVE, we would predict that
21 there would be native retroviral particles in there,
22 as well as endogenous retroviral DNA from the cellular
23 source. In addition, there is a possibility that
24 there could also be potential pseudotypes present due
25 to formation of pseudotypes with the measles vaccine

1 virus and the retroviral sequences.

2 Okay, we used two approaches to analyze
3 the integration question. In one case, we treated the
4 CF supernatant and the MVE samples with DNAse to
5 remove any of the endogenous retroviral DNA sequences.
6 And then the treated inocula was -- then PBMCs were
7 exposed to the treated inocula for 24 hours, and
8 cellular -- and total cell DNA was analyzed by direct
9 PCR for EAV sequences.

10 In another strategy, which would be more
11 specific for analysis of integration, was ALU-PCR.
12 And in this case, we used the untreated inocula CF
13 supernatant or the MVE and exposed PBMCs for 24 hours,
14 and then DNA was prepared and analyzed by ALU-PCR.

15 I'm going to go more into the details of
16 the ALU-PCR when I describe the results.

17 In the next two slides I'm going to
18 describe our results with the first strategy of direct
19 PCR analysis of the DNAse treated samples.

20 Okay, in this slide, which is seeing our
21 analysis of uninfected cells -- do I have a pointer?
22 Okay, in the first lane of each three panels are the
23 uninfected PBMC control DNA with each set of primers.
24 The primers that we used was EAV, and we also used
25 CRE, which is a highly repetitive chicken element, as

1 a control for the DNAse treatment.

2 And we used amphotropic MuLV to

3 demonstrate that a known retrovirus that can infect

4 PBMCs was not affected with the DNAse treatment.

5 In this panel, as you can see, without the

6 DNAse treatment, the EAV primers can detect -- produce

7 a very intense activity, a very intense PCR band.

8 However, after DNAse treatment, we don't detect a

9 band, indicating that this activity -- that this

10 amplification was due to the presence of the DNA and

11 not due to the presence of infections retrovirus.

12 In this case, using the CRE primers, we

13 can also demonstrate that the contaminating cellular

14 chicken sequences are removed with the DNAse treatment

15 and these bands are also seen in the PBMC background

16 of the inoculated DNA.

17 And, as you can see in the ampho, there's

18 no effect of infection with a known retrovirus with

19 and without DNAse treatment.

20 The next slide shows similar analysis

21 using the MVE sample. And, as you can see again in

22 the -- there is high amount of EAV detectable

23 sequences present in the untreated sample. Whereas,

24 upon DNAse treatment of the MVE prior to inoculation

25 of the PBMCs, then this activity is removed.

1 And the results of the CRE indicate that
2 the DNAse treatment worked and that you also remove
3 this contaminating DNA.
4 Because the sample also had measles
5 vaccine present in it, we also analyzed the RNA from
6 the same experiment to demonstrate that there was no
7 affect of DNAse treatment on the ability of the
8 measles vaccine virus to infect the cells.
9 You can see that here with and without
10 DNAse treatment. And also the ampho control shows no
11 effect of the DNAse treatment.
12 So these results indicate that the CF
13 supernatant and the MVE do not contain sequences that
14 can be detected after DNAse treatment upon inoculation
15 of PBMCs.
16 Then, to further confirm these results, we
17 also utilized the ALU-PCR strategy. And first I just
18 want to go over the strategy briefly. And again, this
19 is a very complicated strategy, and I've indicated one
20 of the references that we've used here.
21 In addition, there's another reference by
22 Minami, et al. in Genomics in 1995. And basically,
23 the conditions that we've used are described in those
24 two papers, and we'd be happy to discuss further if
25 anyone wishes to.

1 But the reason we used ALU-PCR is because
2 there are about one million copies per haploid genome
3 of ALU elements in the human DNA. The ALU elements
4 are about 300 bases, and their average occurrence in
5 the DNA is about every three to six KBs.
6 So therefore, if an exogenous sequence
7 integrated into the human genome, there would be a
8 chance that there would be -- that they would
9 integrate upstream or in the vicinity of an ALU
10 element.
11 Therefore, this strategy was utilized to
12 analyze the integration of EAV sequences in the
13 adjacent -- in regions that have ALU elements.
14 As you can see, to do a complete analysis
15 for one retroviral element, you need to use a
16 combination of four sets of primers indicated as A, B,
17 C, D; and the reason being because, for the
18 retrovirus, you need to analyze integration for both
19 of the LTRs.
20 This is the five prime and the three prime
21 LTR, and you need to find out whether this LTR is
22 integrated upstream or downstream of an ALU repeat
23 element, as well as you want to be able to detect the
24 integration in either orientation of the ALU element.
25 So therefore, a combination of using these

1 four primer sets will analyze for integration of a
2 retroviral element located upstream or downstream of
3 an ALU element in either orientation of the ALU
4 element.
5 Now, for simplicity -- for the purpose of
6 simplicity, I'm only going to present limited analysis
7 of our ALU-PCR, but we have done the analysis using
8 all the four sets of primers for each of the samples
9 that I'm going to show you.
10 And also, I should mention that the
11 strategy was optimized based upon the published papers
12 so that the conditions were -- so that the sensitivity
13 was increased and there was -- the conditions were
14 such that there was diminished amplification of ALU-
15 ALU detection, which can also occur.
16 And also we used conditions of long PCR so
17 that we could include any insertions that occurred up
18 to six KBs or more from the ALU element.
19 Okay, these are the results using the
20 control amphotropic MuLV retrovirus. Up here is a
21 diagram showing that two sets of primers were used
22 that would analyze integration of the three prime LTR
23 or the five prime LTR with respect to the ALU.
24 And the results indicate here that, in
25 PBMCs infected with the MuLV shown in lane two, we

1 could see unique bands that were indicative of
2 integration, as compared to the uninfected PBMC
3 control in lane one.
4 Now, one would expect to see more than one
5 band because the integration occurs randomly and the
6 distance with respect to the ALU would be different.
7 And to confirm the origin of these bands,
8 we did sequence this band here and we found, by
9 sequencing, that there was the amphotropic LTR with
10 adjacent spiking sequences and then the ALU element.
11 Then we applied this strategy to analysis
12 of EAV sequences in the measles vaccine equivalent
13 sample, and I'm only going to show you the results
14 from one of the four sets. But using all the four
15 sets, we have no evidence for integration as compared
16 to the control PBMCs.
17 This is an ethydium bromide stained gel
18 showing that, because of the nature of the primers,
19 you can get a smear. However, we see no -- we saw no
20 bands that distinguished the inoculated sample from
21 the uninoculated sample.
22 To further confirm that there were no low
23 level integrants present in this fuzziness, we
24 hybridized with a specific probe and, again, there was
25 no detectable sequences that were specific to the

1 probe. And this is a positive control for the probe.
2 And so these results indicate that --
3 along with the other results that we have, that there
4 is no evidence for integration using the ALU-PCR
5 technique. These are just summarized in the next
6 slide.
7 So basically, I should also mention that,
8 in terms of the sensitivity of the two assays that
9 I've shown, in terms of the direct PCR assay, our
10 sensitivity currently -- we can detect ten copies of
11 EAV sequences.
12 In terms of the ALU-PCR, we can detect 100
13 copies. But we are currently evaluating the limits of
14 detection for each of these assays using relevant
15 standards. We have created a standard for the ALU-PCR
16 that contains retroviral LTR and ALU elements that we
17 have a relevant control for that PCR.
18 So, in conclusion, the data thus far
19 indicates that there is no evidence of integration of
20 EAV sequences in human DNA using the CF supernatant or
21 the MVE, thus indicating the inability of native EAV
22 particles to infect human cells.
23 And our ongoing studies are directed
24 towards doing similar analysis of ALV-related
25 sequences that are present in the vaccine prep, as

1 well as to do extensive characterization, molecular
2 characterization, of the endogenous ALV and EAV
3 sequences in the MVE because we need to understand how
4 representative are our primers with regards to
5 detection of other endogenous retroviral sequences
6 that are present.
7 Basically, there's very limited sequence
8 data available on the EAV sequences, so we need to
9 generate additional data to demonstrate that the
10 primers are representative to that family of
11 sequences.
12 Thank you.
13 CHAIRPERSON FERRIERI: Thank you, Dr.
14 Khan.
15 Because we're ahead of schedule a bit, we
16 do have time for the panel to ask a few questions.
17 Is there any member?
18 Yes, please.
19 For the recording person, it would be
20 helpful if you announced your name first and then she
21 would be able to record that.
22 DR. FOLKS: Yeah, I'm Tom Folks, Centers
23 For Disease Control and Prevention.
24 Couple of questions. You went to a lot of
25 trouble and rigors to get rid of the contaminating DNA

1 from the prep. Did you just look for unintegrated
2 sequences after the infection step of the PBLs?
3 DR. KHAN: Okay, basically we're looking
4 -- in the DNAse treated protocol, we're looking for
5 both unintegrated and integrated because that's total
6 cell DNA. So we would pick up either.
7 DR. FOLKS: Okay, but you used ALU.
8 DR. KHAN: Okay, the ALU is for the --
9 DR. FOLKS: For integrated.
10 DR. KHAN: -- integrated, yes. That is
11 specific for that.
12 DR. FOLKS: Okay, but you didn't show any
13 information where you just looked for unintegrated
14 DNA.
15 DR. KHAN: Okay, the ALU-PCR is directed
16 for integrated DNA. The DNAse treatment and direct
17 PCR analysis would detect unintegrated and integrated.
18 So they're two different procedures. Maybe I'm not
19 clear about the question, or I don't think I've
20 answered it.
21 DR. FOLKS: Well, I mean, you satisfy, I
22 think, by getting rid of the contaminating DNA, you
23 show that. But then do you go and show -- I mean,
24 you've taken a lot of effort now to go to the next
25 step to look for integrated, and I didn't see

1 information that indicated that you still could have
2 some slip through and integrated sequences would be
3 present.
4 DR. KHAN: Yeah, I guess -- again, I think
5 the -- I guess our major concern was for integrated
6 sequences. And I don't know, you know --
7 DR. FOLKS: But the ALU treatment is --
8 study is -- I mean, it works well with MuLV.
9 DR. KHAN: Yeah.
10 DR. FOLKS: But in something that might be
11 much lower at an infectious nature, especially in a
12 pseudotyping scenario, you might have much less
13 integrated material.
14 DR. KHAN: Right, that's why we need to
15 determine the sensitivity, the detection limits, of
16 the ALU-PCR.
17 Again, I should mention that we did select
18 the ALU-PCR strategy to look for specific integration
19 because, in terms of strategies for looking at
20 specific integration, this strategy is more sensitive
21 than others -- for example, inverse PCR.
22 So this is more sensitive in terms of that
23 type of strategy.
24 But just to clarify, in terms of the ALU
25 integration, the sample was not DNAse treated. We're

1 looking at the whole -- we're looking at the native
2 untreated sample. But I agree, I mean, that strategy
3 was not meant to pick up integrated; it picks up
4 integrated, whereas the other one would pick up both.
5 CHAIRPERSON FERRIERI: We have another
6 question from the table.
7 DR. HUANG: From Alice Huang.
8 You mentioned that your PBMC cultures were
9 exposed to the various materials for 24 hours and then
10 you tested them. Did you test for any longer time?
11 Did you go for 48 or 72?
12 DR. KHAN: Yes, actually in my initial
13 studies, which I did not present here, we did do 48,
14 and we also did not find any integration by ALU-PCR.
15 Then I went back to choose 24 in case --
16 you know, we're really looking for effects of
17 nonproductive infection. And I was concerned that
18 maybe, you know, if there was some effect -- some
19 deleterious effect to the cell or something due to an
20 initial integration event, some theoretical effect,
21 that maybe we would be missing it, so therefore we
22 went back to the 24 hours.
23 But longer than that is difficult because
24 the measles vaccine virus itself lyses the culture in
25 about three to four days. And I should mention that

1 the dose that we are analyzing is 40 human doses
2 equivalent, so it's a high dose with regards to the
3 infection.
4 CHAIRPERSON FERRIERI: Any other
5 questions? Anyone from the audience wish to comment
6 or ask a question?
7 Thank you, Dr. Khan, we'll move on with
8 the program then.
9 Dr. Andrew Lewis will begin the series
10 then on the evolving use of animal cells as vaccine
11 substrates.
12 I'm sure we'll take up the slack then.
13 I'll just repeat the rules of our activities here. To
14 speak, you can raise your hand and hopefully I'll see
15 you, and then announce your name, please.
16 Dr. Lewis.
17 DR. LEWIS: Good morning.
18 I'd like to begin the discussion this
19 morning that will occupy us for the rest of the
20 morning by introducing myself to the Committee. I'm
21 Andrew Lewis, the head of the DNA Virus Laboratory in
22 the Division of Viral Products.
23 Before joining CBER in 1995, I spent some
24 years in the National Institute of Allergy and
25 Infectious Diseases studying viral carcinogenesis

1 using adenoviruses, SV40, ANU-SV40 hybrids, as well as
2 a variety of transformed cell lines as experimental
3 models.
4 Since joining CBER, I've had the privilege
5 to work with the organization in the capacity as a
6 head of a group concerned with cell substrate issues.
7 During the past three years, this group
8 has focused on issues associated with
9 xenotransplantation, the presence of reverse
10 transcriptase activity in chicken embryo fibroblasts
11 that Dr. Khan has just reviewed for you, with SV40 as
12 a possible human pathogen, and with issues associated
13 with the possible use of tumor cells as substrates for
14 viral vaccines.
15 It's this issue that will -- that's going
16 to occupy our attention for the rest of the morning.
17 Over the past year or so, CBER has
18 received inquiries and requests about the use of cells
19 derived from human or animal tumors as substrates for
20 viral vaccines to be used prophylacticly in the
21 general population. It's my task, in the next few
22 minutes, to introduce the Committee to the challenge
23 CBER is facing in addressing such requests.
24 In addressing this challenge, CBER is
25 being asked to move beyond the precedent that was

1 established back in 1954 against the use of cell lines
2 established from tumors, especially human tumors, as
3 cell substrates for viral vaccines.
4 A number of factors are motivating the
5 interest in moving beyond the 1954 precedent. I've
6 listed what we consider to be the most important of
7 these factors on the next slide.
8 These factors include the development of
9 whole virus or traditional vaccines to human
10 immunodeficiency virus; bioengineering approaches to
11 viral attenuation in vaccine development; the rapid
12 development of vaccines to emerging viruses such as
13 the H5N1 influenza virus that appeared in Hong Kong
14 last winter; progress in understanding carcinogenesis
15 and in detecting adventitious agents; and finally,
16 experience with highly purified biologicals that have
17 been derived from various types of neoplastic cells.
18 Based on these motivation factors and the
19 fact that CBER must respond to inquiries and requests
20 regarding the feasibility of using tumor cells to
21 develop and produce vaccines for general use, for this
22 morning's presentations we'd like to initiate a
23 dialogue with the Committee that we hope will prove
24 useful in dealing with future issues related to the
25 use of neoplastic cells as vaccine substrates.

1 For my presentation this morning, I'd like
2 to point out that I'm going to use the term
3 "neoplastic cells" quite broadly to refer to all types
4 of immortalized cells, including continuous cell lines
5 that are either non-tumorigenic or tumorigenic, as
6 well as those cell lines that are established from
7 mammalian tumors.
8 As we go forward with the business of
9 addressing the use of neoplastic cells as vaccine
10 substrates, I'd also like to point out that it will be
11 necessary to schedule discussions about specific
12 issues as future meetings with the Committee in closed
13 session.
14 As the presentations today proceed, we'd
15 like the Committee to keep in mind the issues that
16 we'll be asking you to discuss at the end of the
17 talks. These issues are presented in the next slide.
18 Following talks this morning, we'd like
19 the Committee to comment on the approach that we'll
20 review for you in the talks this morning that are
21 being considered in CBER to evaluate the use of
22 neoplastic cells that are proposed for use in the
23 manufacturing of viral vaccines.
24 And we'd also like for you to consider any
25 additional items related to today's presentations or

1 to issues related to the use of vaccines developed or
2 produced in neoplastic cells that the Committee finds
3 appropriate.

4 We thought it would be appropriate to
5 begin our discussions of a change in precedence in the
6 use of cell substrates by first defining for everyone
7 why it's necessary to use animal cells to produce
8 viral vaccines, and then reviewing the types of cells
9 that are currently being used to produce these
10 products.

11 The next slide shows why it's necessary to
12 use animal cells to produce viral vaccines. Viruses
13 in general, as shown in this slide, can be thought of
14 as infectious nucleic acids, either RNA or DNA, which
15 can reproduce themselves only within the context of
16 living cells.

17 Based on these characteristics, viruses
18 can only be isolated and propagated in viable cells.
19 Thus, many of the aspects of a study of viruses,
20 including the development of vaccines to protect
21 humans from viral infections, can only be accomplished
22 using those living cells that are both susceptible to
23 viral infection, as well as viral replication.

24 A critical parameter in the use of living
25 cells for vaccine production is that the cells must

1 not only be able to grow the infecting virus, but they
2 must be able to grow it to sufficient concentrations
3 to make vaccine production feasible.
4 In the next two slides I've listed the
5 types of animal cells that are available to produce
6 viral vaccines. Intact animals that are used to
7 produce vaccines include embryonated chicken eggs to
8 make influenza vaccines, and calves that were used in
9 the past to make smallpox vaccines.
10 The use of intact animals obviously
11 bypasses the need to use tissue culture for vaccine
12 production. Primary cells represent unpassaged tissue
13 culture cells that are established from embryonated
14 eggs or from animal organs.
15 These include cells established from
16 chicken embryos used to produce measles and mumps
17 vaccines, and cells from the kidneys of African Green
18 Monkeys that are used to produce polio vaccines.
19 Diploid cell strains represent cell
20 cultures established from normal human lung tissues.
21 Due to their lack of immortality, these strains should
22 be passage for a limited number of times in cell
23 culture. They are non-neoplastic and they are not
24 tumorigenic.
25 Examples of these cells include the WI38

1 cell strain, the MRC5 cell strain, and the FRhL cell
2 strain. A variety of vaccines are made in these types
3 of cells which include polio, rubella, hepatitis A,
4 rabies and the rotavirus vaccine.
5 Continuous cell lines also represent cell
6 lines to establish some tissue culture from the normal
7 organs from nonhuman primates or rodents.
8 However, continuous cell lines differ from
9 human diploid cell strains, and that, during passage
10 in tissue culture, they become immortal; and therefore
11 they share characteristics with neoplastic cells.
12 In addition, sometime during prolonged
13 tissue culture passage, immortal cell lines can become
14 tumorigenic. That is, the cells from high passage
15 levels will produce tumors when they're injected into
16 susceptible animals.
17 The VERO cell line, established from the
18 normal kidney of an African Green Monkey, is an
19 example of an immortal, non-tumorigenic, continuous
20 cell line. However, VERO cells can become tumorigenic
21 if passage level is greater than 146.
22 Following this, VERO cells will produce
23 progressively growing tumors when they're injected
24 into immunodeficient nude mice.
25 Some polio vaccines are made in VERO

1 cells. The Chinese hamster ovary cell, or CHO cell,
2 and baby hamster kidney cell line 21 represent
3 continuous cell lines that are not only immortal, but
4 tumorigenic as well.
5 Thus far, such cells have been used as
6 substrates only to produce highly purified
7 biologicals.
8 Tumor cell lines represent cell lines
9 established by growing cells from humans or animal
10 tumors in tissue culture. The cells in these lines
11 are immortal and are usually tumorigenic. The only
12 human tumor cell line currently in use to produce a
13 biological is a Namalwa cell line.
14 This cell was established from a B cell
15 lymphoma from a patient with Epstein Barr virus-
16 induced Burkitt's lymphoma. It's used to produce an
17 interferon product that's licensed in Europe.
18 Other continuous cells lines that offer
19 potential as vaccine substrates are normal cells that
20 are transformed in tissue culture into immortal and
21 possibly tumorigenic cells. The 293 line of
22 adenovirus transformed human kidney cells in the COS-1
23 line of SV40 transformed African Green Monkey kidney
24 cells are representatives of these types of cells.
25 There are currently no licensed products

1 that are made in virus transformed cells.

2 The use of embryonated eggs in cells grown
3 in tissue cultures to produce vaccines has evolved
4 slowly over the past 60 years.

5 With the discussions today in their
6 historical perspective, in the next two slides I
7 review for you some of the important events in the
8 development of cell substrates for vaccine production
9 that have occurred during the past 60 years.

10 In 1933, Drs. Woodruff and Goodpasture
11 grew the fowlpox virus on the chorioallantoic membrane
12 of embryonated chicken eggs. Subsequent work found
13 that the embryonated chicken eggs were susceptible to
14 a wide variety of viruses.

15 And as I've shown you on the previous
16 slide, influenza, yellow fever, smallpox vaccines, as
17 well as the vaccine for horses against
18 encephalomyelitis virus, were all developed in the
19 embryonated chicken egg before 1950.

20 The innovations of Woodruff and
21 Goodpasture were followed 16 years later with a
22 demonstration by Enders, Weller and Robbins in 1949
23 that polio viruses would grow and produce virus-
24 specific changes in human kidney cells growing in
25 tissue culture.

1 This study introduced the first reliable
2 method to grow viruses in test tubes, set the stage
3 for the tissue culture era of virology, and provided
4 a major breakthrough in the growth of viruses for
5 vaccine production; a breakthrough that I don't need
6 to remind you that we're still exploiting today.
7 In 1953, the first lots of inactivated
8 polio vaccine were produced in rhesus monkey kidney
9 cells.
10 And in 1954, in response to the need to
11 develop adenovirus vaccines to protect military
12 recruits in boot camp against acute respiratory
13 disease, the Armed Forces' Epidemiology Board met and
14 determined that only normal cells were acceptable as
15 substrates for viral vaccines, thus establishing the
16 precedent that we're addressing today.
17 In 1961, Hayflick and Morehouse described
18 the long term culture of human diploid cell
19 fibroblasts, showed that such cells were susceptible
20 to polio virus infection, and initiated the
21 discussions that human diploid cells might be more
22 suitable for vaccine production than primary cells
23 from animal organs.
24 In 1967, the World Health Organization
25 Committee on Cell Culture accepted human diploid cells

1 as substrates for vaccine production. In this same
2 year, Van Wezel grew cell lines on microcarriers, a
3 technique that greatly expands the surface area
4 available for cell growth in any culture container.
5 In 1977, interferon was produced in
6 concentrations sufficient to be clinically useful
7 using cultures of lymphoblastoid cells obtained from
8 human B cell lymphomas. And in 1978, the possibility
9 of using continuous cell lines as substrates for
10 biologicals was introduced at a meeting at Lake
11 Placid, New York.
12 In 1981, Montagnon, Fanget and Nicolas
13 produced the polio vaccines using viral cells grown in
14 microcarrier cultures. In 1987, the World Health
15 Organization accepted the use of continuous cell lines
16 for the production of highly purified biologicals and
17 biotechnology products, including the polio vaccine.
18 And now, in 1998, we're confronted with
19 new technological advances and the need to pursue the
20 development of all types of HIV vaccines. This makes
21 it necessary to consider how to approach the use of
22 continuous cell lines and tumor cell lines as possible
23 substrates of viral vaccines.
24 And in the late 1970s and early 1980s,
25 when confronted not only with the ability to produce

1 therapeutically useful amounts of interferon for
2 Epstein-Barr virus-induced human lymphoblastoid cells,
3 but the potential to use hybridoma technology to
4 produce therapeutically useful quantities of
5 monoclonal antibodies and the ability to develop a
6 wide variety of products using recombinant DNA
7 technology, regulatory agencies were challenged to
8 weigh the need for these new products with the
9 possible risks that were associated with the use of
10 continuous cell lines derived from normal tissues and
11 cell lines derived from animal tumors to produce these
12 products.

13 The question was, how to proceed? A
14 successful approach evolved over a period of about ten
15 years, and patients are now benefitting from a variety
16 of products made possible by a combination of these
17 scientific and regulatory innovations.

18 The innovations in regulatory review that
19 permitted the clinical use of highly purified
20 biologicals produced in continuous cell lines was
21 based on the considerations that I've listed in the
22 next slide.

23 This approach was based on the following
24 points. First, those concerns that were specifically
25 associated with the use of continuous cell lines were

1 identified.

2 These concerns included the possible
3 presence of adventitious agents and the possibility of
4 transferring abnormal biological characteristics to
5 recipients by way of occult viruses, residual cellular
6 DNA, or residual cellular proteins.

7 Methods were needed -- or they were needed
8 and developed to address each of these concerns
9 theoretically and experimentally. These methods were
10 then applied to develop estimations of the risk posed
11 by the concerns.

12 And finally, these concerns and methods
13 were addressed and developed in scientific forums.

14 In considering how to approach the use of
15 continuous cell lines and cells derived from tumors as
16 substrates for traditional vaccines, we've reviewed
17 the approach that was used in managing the regulatory
18 issues associated with the introduction of continuous
19 cell lines as substrates for highly purified
20 biologicals.

21 Following my talk, Dr. Sheets will present
22 a more comprehensive outline of this approach, and
23 then Dr. Clouse from the Office of Therapeutics will
24 review the experience with this approach in evaluating
25 biotechnology products.

1 The success with the introduction of the
2 use of continuous cell lines provided an example of
3 how to approach the new regulatory challenge of
4 evaluating the use of neoplastic cells as vaccine
5 substrates.
6 Using this example, we are considering the
7 approach I've outlined in the next three slides. The
8 approach consists basically of five components. We'll
9 begin with the process similar to that initiated in
10 1987 to evaluate continuous cell lines.
11 To begin this approach, it's first
12 necessary to identify the specific issues that need to
13 be addressed. I'm going to outline these issues that
14 are related to the use of neoplastic cells in the
15 slides that follow this one.
16 Once the issues are identified, the next
17 step is to develop theoretical and experimental
18 methods to evaluate each issue. Dr. Krause is going
19 to outline some of these methods in his talk later
20 this morning.
21 To make the development of methods to
22 evaluate each issue useful for regulatory purposes,
23 it's necessary to develop criteria to establish the
24 possible level of risk associated with each issue. In
25 addition to developing a plan, it's necessary to

1 discuss and develop not only the concepts, the issues,
2 but all aspects of any approach in public scientific
3 meetings and workshops.
4 The specific issues that are associated
5 with the development of tumor cells as vaccine
6 substrates we've tried to present in the next two
7 slides.
8 In this table, I've listed the general
9 issues in the left-hand column, the nature of the
10 concerns that are generated by these specific issues
11 in the middle column, and references to data that
12 generated the concern in the column on the right.
13 In developing a table, we reviewed, as
14 best we could in the time available, the literature
15 dealing with possible risk related to neoplastic cells
16 as vaccine substrates. The table was then constructed
17 by listing all of those issues that would appear to
18 have raised concerns.
19 Such a comprehensive list is based on the
20 idea that it was essential to begin our approach from
21 as broad a base as possible, as any issue judged to be
22 irrelevant could be considered and dismissed. This is
23 the complex slide.
24 And time doesn't permit, and it's not our
25 purpose today, to present a detailed review of each

1 issue in the scientific documentation of why it's
2 included in the table. Many of these issues will be
3 the subject of detailed discussions at future
4 meetings.

5 Today I'm only going to mention the
6 general issues and the specific concerns that are
7 related to them, and very briefly mention why it's
8 necessary to define some of these concerns.

9 As you can see, the first general issue
10 includes tumor cell contamination with the possible
11 induction of tumor allografts. At first glance, this
12 concern may seem trivial, as it's quite easy to
13 document the removal of viable cells from vaccines.

14 What is noted in Southam & Gross, human
15 tumor cells have, on very rare occasions, been grafted
16 into allogeneic humans. So of course it's going to be
17 important to demonstrate and document that any vaccine
18 produced in a neoplastic cell contains no such
19 neoplastic cells.

20 Adventitious agent contamination with the
21 possible transfer of known or unknown infectious
22 agents is a concern for all biologicals and probably
23 doesn't need any further discussion.

24 The formation of recombinants between
25 vaccine virions and adventitious viral agents present

1 in cell substrates occurred in adenovirus vaccines
2 that were prepared in rhesus monkey kidney cells in
3 the 1950s.
4 Before the discovery of SV40 in 1960,
5 humans were immunized with adenovirus vaccines that
6 contained adenovirus SV40 hybrid viruses. The rate of
7 recombination between adenoviruses and SV40 in monkey
8 cells is not known; nor do we know anything about the
9 ratio between the hybrid and non-hybrid adenovirions
10 that were present in any of the vaccine preparations
11 that were used at that time.
12 As recombination among a variety of
13 viruses and cells co-infected in tissue culture, it is
14 not uncommon. This is an issue that certainly will
15 need further consideration.
16 The possible activation and transfer of
17 occult or unusual agents as a consequence of vaccine
18 production in neoplastic cells is a complex topic.
19 Studies have shown that prolonged passage in tissue
20 culture can induce the expression of endogenous
21 viruses.
22 And other studies have shown that viruses,
23 especially retroviruses, can parasitize the genome of
24 large DNA viruses such as herpes viruses. The
25 efficiency with which such events might occur in

1 neoplastic cells and in vaccines is unknown.

2 An unusual viroid-like agent has been
3 associated with transmittal of a lymphoma in Syrian
4 hamsters. Epidemics of infectious lymphoma have
5 occurred in several different hamster colonies.
6 Whether such agents are present in humans is unknown.

7 Continuing down the list, we have
8 contamination with cellular DNA and the possible
9 transfer with this DNA of oncogenic or infectious
10 genetic information in the form of activated
11 oncogenes, integrated viral oncogenes, or viral
12 genomes, as well as proviruses.

13 Dr. Krause will have more today about
14 evaluating this concern in his talk later this
15 morning.

16 Now, based on recent developments in the
17 fields of transmissible spongiform encephalopathies,
18 when considering the presence of residual cellular
19 materials, the possible transfer of residual cellular
20 proteins containing prions must be considered.

21 In addition to these issues, the
22 possibility that vaccine virions will package cellular
23 nucleic acids or rescue integrated viral genomes or
24 pseudotype endogenous retroviruses with an efficiency
25 that could lead to the transfer of biologically

1 relevant quantities of oncogenic genetic information
2 needs to be considered as well.
3 The possibility that the instability of
4 the genome of the neoplastic cells growing
5 continuously for long periods of time in tissue
6 culture might enhance any of these events must also be
7 weighed.
8 Now, in assessing how to address the
9 variety and complexity of the issues that need to be
10 considered in managing proposals to use neoplastic
11 cells as vaccine substrates, the most important
12 consideration, of course, is how to develop methods to
13 measure risks and use those measurements to evaluate
14 product safety.
15 Our approach to the safety issue is to
16 look at the possibility of assessing the level of risk
17 posed by each concern quantitatively, establishing the
18 chance of occurrence or the probability of a worst
19 case scenario for each, and using such data to weigh
20 the relative risk of any product produced in
21 neoplastic cells.
22 The approach we are considering is
23 presented in the next slide.
24 To simplify the discussion, we're
25 designating this a defined risks approach. What we're

1 proposing is that a defined risk approach could
2 accomplish the goal of providing a quantitative
3 estimate of the level of risk posed by each concern,
4 as well as a means of quantifying the overall, or
5 cumulative, level of risk posed by the product itself.

6 Establishing both concern associated risk
7 levels and cumulative risk levels will then provide
8 methods to better judge the suitability of any product
9 for the public health situation it's designed to
10 alleviate.

11 And again, in his talk later this morning,
12 Dr. Krause is going to address this aspect of our
13 approach in more detail.

14 Now the manner in which we plan -- or we
15 would hope to implement such an approach to evaluating
16 regulatory issues associated with proposals to use
17 neoplastic cells as substrates for vaccines is
18 presented in the last slide.

19 To implement this plan, we would hope to
20 review the problem and develop a working document that
21 outlines the issues and concerns and how they may be
22 addressed. We would hope to hold workshops on the
23 issues and possibly have the document be the subject
24 of one or more discussions at those workshops or of a
25 workshop independently devised to consider the

1 document itself.

2 The document would then be revised based

3 on the outcomes of these discussions, and it would be

4 presented to the Committee, this Committee, for review

5 and comment. Following those discussions, we would

6 hope that CBER could develop some more formal policy

7 on the use of tumor cell lines as vaccine substrates.

8 This is the end of what I have to say.

9 I'd be happy to try to address any questions you might

10 have before I turn the podium over to Dr. Sheets.

11 CHAIRPERSON FERRIERI: Thank you, Dr.

12 Lewis.

13 I guess I would caution the panel that,

14 because it is an open session, that there may be some

15 questions Dr. Lewis will be unable to answer if

16 they're too specific and deal with proprietary issues.

17 Dr. Greenberg.

18 DR. GREENBERG: Andy, thank you for a very

19 organized look at this.

20 When you're defining risk, it seems to me

21 that perhaps you want to define it compared to a

22 standard. And wouldn't your standard be your diploid

23 cells and risk would be the increased risk above and

24 beyond what we have already determined to be

25 acceptable?

1 DR. LEWIS: Dr. Greenberg, the definition
2 of what is an acceptable and an unacceptable risk, I
3 think, is an issue that will create considerable
4 discussion. At this point in time, I think that we're
5 not at a stage where we can answer that question with
6 any confidence.
7 And I think that risk is going to be a
8 shifting target. It's going to depend on the nature
9 of the product, the nature of the problem the product
10 is designed to alleviate, and the complexities of the
11 individual concern that that risk is attempting to
12 measure.
13 I think the concept at this point in time
14 is that we would hope to be able to use experimental
15 data to define what has been -- what the risk might be
16 and how it has been altered as a result of the
17 manufacturing process, or at least addressed, and then
18 be able to use that to estimate what the risk factor
19 might be.
20 Beyond that, I think it's very hard to get
21 a handle on it without further consideration. So I
22 don't really think I can answer your question
23 satisfactorily is what I'm trying to say.
24 CHAIRPERSON FERRIERI: Dr. Adimora.
25 DR. ADIMORA: People have a variety of

1 concerns about vaccines, people being the general
2 public. To my knowledge, the cell substrates in which
3 the vaccines are grown has not been one of their
4 concerns, one of their major concerns, to date.
5 But I was -- but it conceivably could be
6 in the future, particularly if continuous -- if other
7 continuous cell lines are used or tumorigenic cell
8 lines are used more frequently for vaccines.
9 And I was wondering what you thought about
10 that, about the potential for the public's concern,
11 and if there were going to be any ways to address any
12 potential concerns?
13 DR. LEWIS: I think that, in contrast to
14 what you say, there has been tremendous concern over
15 the history of cell substrates both in the public and
16 in the scientific community about the introduction of
17 new -- of the use of any substrate and the
18 introduction of new substrates.
19 There was a tremendous concern associated
20 with the polio vaccine that was developed in rhesus
21 monkey kidney cells associated with SV40, the SV40
22 infection. Two years ago we were one of the sponsors
23 of a meeting that were dealing with the follow up to
24 those concerns.
25 Those concerns continue today. The

1 introduction of the diploid cell strain was
2 accompanied by a ten year -- a more than ten year
3 debate on the safety of using human cells as a
4 substrate for vaccines.
5 So there's -- anytime a new substrate has
6 been proposed, it's a major alteration in our thinking
7 and requires -- and has generated considerable
8 concern. Now, sometimes this concern has reached the
9 public through the media; sometimes it has not.
10 DR. ADIMORA: Well, see, that's what I was
11 talking about. I'm aware that there's been tremendous
12 concern on the part of the scientific community, but
13 maybe I've missed -- I guess I must have missed it,
14 but I hadn't been aware of tremendous amounts of
15 concern in the general media on the part of the
16 general public, and there conceivably could be much
17 more than there already has been.
18 That's what I was referring to. I'm aware
19 of the scientific community.
20 DR. LEWIS: Well, I think there has been
21 in the past. Now, what happens in the future, we'll
22 have to see.
23 CHAIRPERSON FERRIERI: Other questions?
24 Dr. Snider.
25 DR. SNIDER: Dixie Snider.

1 Andy, thanks a lot for that very nice
2 presentation.
3 It seems to me that there may be some
4 assumptions that are being made in taking this
5 approach, and it would be useful to make them
6 explicit. Because if we're talking about a new cell
7 substrate, the issue comes up is how do you decide on
8 whether to use a new substrate rather than an old one.
9 And there, it's not only just the ability
10 of your virus, let's say, to grow in that substrate,
11 but how efficiently it does that, and so you get
12 involved in some cost.
13 And I'm just wondering how the model takes
14 those things into account, because most of the things
15 you talked about really focus on we have already made
16 a decision to assess a new substrate, and it seems to
17 me it skips over a couple of questions.
18 DR. LEWIS: I don't think that I meant to
19 give the impression that any of this is cast in stone.
20 What we're trying to do is develop an approach for
21 purposes of discussion that can be used as a target to
22 shoot at.
23 I don't think there have been any concrete
24 decisions to implement anything that I've said at this
25 point in time.

1 DR. SNIDER: Okay, well, I mean, I guess
2 my suggestion then would be that somehow in the model,
3 as it moves along, some criteria be established on
4 when it would be appropriate to even begin to talk
5 about a new cell substrate as opposed to an older one.
6 What would be reasons to move to a new
7 substrate as opposed to one that's already been
8 extensively used for which we have, presumably, fairly
9 extensive safety data?
10 DR. LEWIS: I think we have to deal with
11 the requests that are made to the organization for a
12 regulatory consideration. And so I think that our
13 response to that -- what we have to do is respond to
14 those requests.
15 And we're trying to develop some sort of
16 systematic approach to think about how to respond to
17 those requests.
18 The substrate that's used by the
19 manufacturer will, of course, depend on those two
20 things that you said. First of all, it has to -- the
21 virus has to replicate and has to be of sufficient
22 quantity to make the product useful.
23 And the safety issues would then have to
24 be considered based on the nature of that material.
25 We would hope that they would select materials that

1 would be more amenable or pose less of a risk, but
2 that may not always be the case.
3 But we can't -- we have no way of
4 advising, I think, against what they do at this point
5 in time.
6 Dr. Hardegree or Dr. Eagan, would you all
7 like to comment on that aspect of the selection
8 process?
9 DR. HARDEGREE: I think some of this
10 discussion may best follow some of the points that Dr.
11 Sheets may want to make. But I think it's fair to say
12 that we are facing these issues now.
13 I mean, we would -- Andy has posed the
14 development of some papers and some applications
15 through workshops, but we are being faced with new
16 cell substrate usage everyday with different products.
17 And we are obviously in -- not at the
18 point of considering licensure of those products, but
19 some small Phase I studies may be underway with some
20 of the cell substrates that are being talked about,
21 and are certainly being talked about globally.
22 These are not just issues related to the
23 U.S. The WHO is also facing this issue and wanting to
24 continue this discussion through workshops as well.
25 And I think that this is the purpose of getting this

1 out today, is to try to get some of the points that
2 you believe that we need to address on the table.
3 CHAIRPERSON FERRIERI: Thank you.
4 DR. SNIDER: I don't want to belabor this
5 too much, but it does seem to me that, although FDA
6 can't tell the manufacturers what to do, and
7 shouldn't, that some discussion and perhaps some
8 guidance might evolve from the meetings you're talking
9 about with regard to some of the trade offs.
10 Because, after all, if we're talking about
11 a cell line that has an extensive safety record and
12 only a slightly higher yield, let's say, on the new
13 substrate and so forth, then one might be inclined to
14 go -- to encourage the use of the more traditional
15 substrate, is the only point I was getting at on that.
16 The other point I wanted to make is I
17 think, in thinking broadly about this, this is not to
18 downplay any of the things that you're talking about
19 here, but I think inevitably these issues -- some
20 issues are going to emerge after the fact.
21 Some new scientific data is going to
22 become available or some claim is going to be made.
23 And so the post marketing surveillance aspect of this
24 I bring up again as something that we really have to
25 pay attention to and try to ensure that we have

1 adequate resources for.

2 CHAIRPERSON FERRIERI: Much of this will
3 be quite appropriate as we go into the big discussion
4 after the presentation. So we have time for two other
5 questions. Two people already had up -- had their
6 hands up. Dr. Kohl and then Dr. Daum.

7 Steve.

8 DR. KOHL: Steve Kohl.

9 Thank you again, Dr. Lewis, for your
10 presentation.

11 It strikes me that many of the issues
12 you've raised in your two issue tables don't
13 necessarily strictly apply to tumorigenic lines. I
14 mean, these are concerns that, if anything, are maybe
15 even heightened in whole animal use, in primary cell
16 lines.

17 And I think it's very important that this
18 not be seen as a giant leap into a great unknown area,
19 but as our improved understanding of risks that we've
20 actually been dealing with for years and years
21 sometimes without knowing it.

22 DR. LEWIS: I'd say absolutely.

23 CHAIRPERSON FERRIERI: Dr. Daum.

24 DR. DAUM: I think that we've clearly been
25 focusing -- well, we have been focusing almost

1 exclusively on this issue of risk. And I think that
2 the questions that people are looking for feedback on
3 are both scientific and, ultimately, as someone raised
4 over here, social issues as well.
5 But I think there's more than risk to deal
6 with here because there's also an issue of benefit.
7 And I think that there's a variety of very real
8 concerns that you pointed out so nicely in your
9 presentation, and then comes width between the lines
10 on many of your slides a number of theoretical
11 concerns.
12 There's probably lots of things about
13 these processes and these new ideas about how to make
14 products and vaccines that we don't know much about.
15 And I would submit that it's impossible to know, a
16 priori, where all those potential problems are.
17 And the corollary of that, or the
18 inference from that, is it's impossible to really
19 accurately gauge what the risk is. And I'd like to at
20 least introduce the idea that, while it's tempting to
21 say let's not take any risk and come to the idea of
22 let's not use neoplastic cells for anything, I think
23 we also need to keep an eye on the potential benefit.
24 And the thinking about risk and benefit
25 will certainly evolve as ideas -- we allow the

1 scientific and social communities to go forward with
2 thinking about this.
3 To just conclude with one example that I
4 think was really helpful, at least for me to think
5 about, is when there were 30 or 40 or 50,000 children
6 in a year being paralyzed each year by polio, I think
7 people would have been willing to take some risks, if
8 you will, with development of a vaccine quickly and
9 get it on the market.
10 And, in a sense, that's what happened.
11 The trade off is that there's a few cases of vaccine-
12 associated paralytic polio. Would someone 40 years
13 ago have been willing to trade the 50,000 for six or
14 eight? Of course they would.
15 And then the thinking evolves to another
16 point where the 50,000 are gone, and now we say it's
17 socially unacceptable to have these six or eight. We
18 have a new problem that we want to deal with together.
19 So I think the thinking about what is risk and what is
20 benefit is going to evolve with each idea that you
21 introduce.
22 And it's important, I think, that we look
23 at the benefit as well as considering the risk at the
24 same time.
25 CHAIRPERSON FERRIERI: One last question.

1 Dr. Wolfe, please.

2 DR. WOLFE: When I was asked to come to
3 this meeting, I was told that it has arisen because of
4 some pending applications, the details of which
5 there's no need to discuss this morning. But I'd just
6 like -- at the risk of continuing the belaboring that
7 Dr. Snider mentioned, I agree with the point he's
8 making.

9 A very thoughtful process has just been
10 laid out involving public discussion, a draft of some
11 proposals, revising it and everything. And what I'm
12 concerned about is that the thoroughness and careful
13 consideration of this process may get affected by the
14 need to respond to these pending applications.

15 As you all know, in parts of the FDA there
16 are these prescription drug user fee set deadlines.
17 Tomorrow is a deadline for some product that's been
18 submitted for treating diabetes, for example, and they
19 have to respond.

20 And my own knowledge is much more in the
21 area of prescription drugs than biologics, and the
22 question I have really is, is the thoughtful process
23 you're talking about, which I think needs to be gone
24 though -- in addition to the point that Dr. Snider
25 made is, what is on the benefit side, the point you

1 just raised -- exactly what is the benefit to be
2 derived from leaping off of this 40-some year old, 50-
3 some year old dictum about we shouldn't be using human
4 tumor cell lines?

5 Is this process going to be artificially
6 speeded up and made less thorough because of these
7 pending applications or not? And this is a question
8 really for the regulators, and maybe it's going to be
9 discussed later. But I'm very worried about that
10 because I think that -- with or without these specific
11 applications having been filed, it's a matter worth
12 discussing and worth discussing very carefully.

13 And it may take a long time both to answer
14 the question is there clear evidence that we are
15 willing to take some measured risk because of the
16 clear evidence of the benefit, and not just an
17 economic benefit that you can produce these things
18 faster and cheaper, which is a benefit, to be sure,
19 but other kinds of benefits.

20 I'm just worried about the whole time
21 frame of this because it is propelled now by these
22 pending applications.

23 DR. LEWIS: I think the only way that I
24 can respond to that, based on what I reviewed, is that
25 every time these discussions are introduced about

1 changing substrates, there is a substantial debate.
2 The introduction of the diploid cell, that
3 took ten years. It took ten years to get continuous
4 cell lines together. And I think it's very unlikely
5 that anything precipitous would happen here under any
6 circumstance.
7 The regulatory process certainly has its
8 deadlines, and they have to be addressed, but safety
9 is the issue here. And the regulatory process, at
10 least from my perspective, has to be convinced that
11 safety is being met, and I think that would be the
12 overriding concern.
13 CHAIRPERSON FERRIERI: I'd like to see --
14 DR. LEWIS: So I think it could be
15 precipitous, but it's unlikely.
16 CHAIRPERSON FERRIERI: Dr. Hardegree, did
17 you want to say something?
18 DR. HARDEGREE: I think it's important
19 that we're talking about time lines that differ from
20 -- when we have to deal with IND processes, we have to
21 think about the time lines that we need and whether or
22 not materials can go forward, whether they go on hold
23 because of safety issues, whether we have an adequate
24 information base for that.
25 For the license application, we have user

1 fee deadlines as well that are dealing with the review
2 process. And I have to emphasize that it is an
3 obligation to review and not approve. So that we have
4 to be certain that the products that we are looking at
5 are safe and effective based on the material that has
6 been submitted.
7 And if we need to do additional cycles of
8 review after we do our initial reviews within the time
9 lines, then that's what we have to do.
10 CHAIRPERSON FERRIERI: I think we can
11 amplify some of these issues when we go into the
12 longer discussion period.
13 Thank you, Dr. Lewis.
14 We'll move on to the presentation by Dr.
15 Becky Sheets from FDA on evolving cell substrate
16 issues as they pertain to investigational vaccines.
17 And she's going to use a high tech presentation here,
18 I see.
19 DR. SHEETS: Good morning.
20 I think that a lot of the questions that
21 were brought up just now in the discussion I'm going
22 to be addressing in my talk, so hopefully you'll find
23 answers. If not, I'm sure we can have further
24 discussion.
25 Good morning. I'm Rebecca Sheets, and I

1 work in the Viral Vaccines Branch of the Applications
2 Division in the Office of Vaccines at CBER.
3 Today I will be presenting to you the
4 safety and regulatory issues concerning cell
5 substrates for the production of viral vaccines, and
6 providing you with an example of how CBER has begun to
7 address these issues for novel substrates proposed by
8 manufacturers.
9 CHAIRPERSON FERRIERI: Excuse me, Dr.
10 Sheets. We need to have the slides moved up some.
11 Is there someone here who can adjust the
12 machinery?
13 DR. SHEETS: I'm not sure -- we've already
14 put it on --
15 CHAIRPERSON FERRIERI: That's as high as
16 it can go?
17 DR. SHEETS: -- the Tower of Babel.
18 CHAIRPERSON FERRIERI: Can the audience
19 see the slides?
20 PARTICIPANT: Sixty percent.
21 CHAIRPERSON FERRIERI: Well,
22 simplistically, if you just add something underneath
23 it, it will raise the slides.
24 DR. SHEETS: Is that a little bit better?
25 CHAIRPERSON FERRIERI: Not really; not for

1 everyone in the room. It has to be higher. Let's
2 move that back a little and it's -- it's getting
3 better. You're working in the right direction.
4 This is the best use of Holiday Inn
5 crockery that I've ever seen.
6 (Laughter.)
7 How does the audience feel about this now?
8 Great.
9 PARTICIPANT: It looks relatively safe.
10 DR. SHEETS: That's important. I don't
11 want to lose this important Government property here.
12 Okay, I'll continue. Next slide, please.
13 No, back one. Page up. Thank you.
14 The authority that CBER has for regulation
15 of investigational vaccines is provided according to
16 Title XXI of the Code of Federal Regulations in Part
17 312. This regulation grants CBER the authority to
18 ensure product safety before investigations can be
19 conducted in humans.
20 CBER does not have the authority to
21 dictate to sponsors what product they should
22 manufacture or in which cell substrate they should
23 manufacture it. And CBER must provide guidance to
24 sponsors on how to demonstrate safety.
25 It is also important to understand that

1 CBER licenses products for intended uses or
2 indications. CBER does not license cell substrates
3 per se; nor, for that matter, adjuvants per se.
4 These are components, or raw materials,
5 used in the manufacture of products. It is the final
6 product that has been demonstrated to meet an intended
7 use which is licensed by FDA, and each product is
8 reviewed on a case by case basis.
9 Next slide.
10 Guidance for industry is currently
11 available for characterization of cell lines used to
12 produce biological products. In addition to the 1993
13 so-called "Points To Consider" document published by
14 CBER, some viral vaccines, specifically those not made
15 in primary cells, are covered by guidance promulgated
16 in 1997 by the International Conference on
17 Harmonization, or ICH, in the Q5D document.
18 Neither of these documents specifically
19 address the use of transformed or tumor derived cell
20 lines. Rather, they address the use of diploid cell
21 strains and continuous cell lines. I'll describe the
22 differences between these substrates shortly.
23 Next slide.
24 But first, what is meant by
25 characterization of cell lines? Each manufacturer

1 must characterize the cell substrates banked and used
2 in production in their own facilities. This includes
3 a description of the history of the isolation and
4 banking of the cell substrate.
5 The isolation may have been performed
6 prior to the manufacturer's receipt of the substrate.
7 Also, they should provide the description of how they
8 prepared cell banks. They should describe the growth
9 characteristics of the cells, and they should test the
10 cells to determine the karyology and tumorigenicity.
11 Importantly, they must assess their cell
12 banks for freedom from adventitious agents. I'll
13 describe this further.
14 Next slide.
15 Tests to be performed to characterize cell
16 banks include the determination of the karyology of
17 the cells. Furthermore, tumorigenicity is assessed by
18 injecting cells into immunosuppressed rodents to
19 monitor tumor formation.
20 Colony formation in soft agar can also be
21 assessed. These tests apply to cells which are not of
22 rodent origin, as all continuous cell lines of such
23 origin are tumorigenic.
24 Next slide.
25 Adventitious agent tests include those for

1 bacterial and fungal sterility; cultivatable and non-
2 cultivatable mycoplasma; and for insect cells,
3 spiroplasma. And when appropriate, mycobacteria can
4 be detected in guinea pigs or culture.
5 Finally, viruses can be detected by in
6 vitro and in vivo tests, specifically viruses such as
7 those which cause acute or lytic infections, and those
8 which cause latent infections like retroviruses and
9 other oncogenic viruses.
10 Some of these adventitious agents are
11 readily amenable to detection, such as bacterial and
12 fungal sterility. Some are more difficult to detect,
13 but well established methods for detection are
14 available, such as mycoplasma or acute viruses.
15 And some are problematic to detect by
16 currently validated detection assays.
17 Next slide.
18 Tests for adventitious viruses include
19 those performed in vitro. Monolayer cultures of at
20 least three cell types are used, including cells of
21 the same species and tissue type as the cell substrate
22 being tested, human diploid cells and monkey kidney
23 cells.
24 These cultures are assessed for
25 hemadsorption and hemagglutination at the end of the

1 culture period. Also, if the growth medium or other
2 components to which the substrate is exposed are
3 animal derived, then tests should performed on the raw
4 materials according to Title IX of the CFR, Part 113.
5 Furthermore, bovine derived products
6 should be certified to have been obtained from herds
7 free from bovine spongiform encephalopathy.
8 Next slide.
9 Tests for adventitious agents also include
10 those performed in vivo in adult and suckling mice; in
11 embryonated hens eggs; and, when appropriate, in
12 guinea pigs, rabbits and/or monkeys.
13 Next slide.
14 Additional tests may be required. For
15 rodent substrates, antibody production tests in mice,
16 rats or hamsters (referred to as MAP, RAP or HAP
17 tests) are performed. Also, an infectivity test to
18 detect lymphocytic choriomeningitis virus, or LCM,
19 should be performed.
20 For human substrates, it may be
21 appropriate to screen for Epstein Barr virus,
22 cytomegalovirus, or hepatitis B or C viruses by in
23 vitro techniques such as PCR. The appropriateness of
24 these tests is supposed to be considered on the basis
25 of the tissue source and donor medical history.

1 Next slide.

2 Also, when appropriate, tests for
3 oncogenic or latent viruses should be considered to
4 detect papilloma viruses, adenoviruses and herpes
5 viruses.

6 Finally, and importantly, tests for
7 retroviruses must be performed. These tests include
8 transmission electron microscopy, assays to detect
9 reverse transcriptase activity, and infectivity
10 assays.

11 Next slide, please.

12 When CBER reviews an IND for a viral
13 vaccine, we make safety evaluations based on several
14 considerations. We consider the intended use. Is the
15 product intended for prophylaxis or therapy? What is
16 the target population?

17 For example, is the sponsor intending to
18 use the product in healthy infants? What is the route
19 of administration of the product? Is it to be given
20 parenterally or mucosally (for example, intranasally
21 or orally)?

22 How many doses will be given cumulatively?
23 And what is the severity of the disease being
24 targeted? Is the medical need currently unmet?

25 And finally, we consider safety on the

1 basis of whether the substrate is intended for
2 production of the final product, or was used in the
3 history of product development (for example, in the
4 isolation or passage of viral seeds).
5 Next slide, please.
6 We also consider safety of the product on
7 the basis of the extent of purification, or viral
8 clearance, during production. Many viral vaccines are
9 simply culture supernatant harvested from the
10 production cells and sterile filtered.
11 Some products, however, undergo
12 significant purification procedures.
13 Furthermore, we consider the extent of
14 inactivation of the product. Live viral vaccines
15 undergo no inactivation because the vaccine virus
16 itself would be inactivated and thus rendered
17 ineffective.
18 In contrast, inactivated vaccines undergo
19 significant inactivation procedures which can be
20 validated to destroy infectivity of both the vaccine
21 virus and many potential adventitious viruses.
22 Next slide.
23 CBER takes into account the whole history
24 of potential exposures of the final product to animal
25 derived substances when considering product safety.

1 Safety is considered on the basis of the substrate
2 used for production.
3 What is the source species, and what
4 contaminants could have come from that species? And
5 what exposures would have occurred during production?
6 For example, could human operators expose the cell
7 substrate to human viruses, and is the substrate
8 susceptible for replication of those viruses?
9 We consider the raw materials used in
10 production such as any antisera used for selection or
11 purification, and medium components used in cell
12 cultures such as serum or trypsin.
13 Are these raw materials animal derived,
14 and what are the source species? What contaminants
15 could have come from those species? And we consider
16 the passage history of the viral seeds, including the
17 cell substrates in which they were isolated and
18 passaged, and the raw materials to which they were
19 exposed during isolation.
20 The viral seeds may be isolated in cells
21 different from those used in production, and they may
22 have been passaged through several different species
23 cells for the purpose of attenuation.
24 We consider all of these exposures in
25 product safety considerations.

1 Next slide, please.

2 The types of cell substrates, which are
3 the focus of today's discussion, include continuous
4 cell lines, which are cells which have survived
5 extended culture passages and do not senesce. Thus,
6 they're considered to be immortalized.

7 Such cell lines can be banked, unlike
8 primary cells, and thus can be characterized.
9 Proposals have also been made to use transformed cell
10 lines such as 293 cells which are derived from a human
11 embryonic kidney, but then transfected with adenovirus
12 Type 5 sequences which transform them to become
13 tumorigenic.

14 Tumor derived cells have also been
15 proposed either for production or for isolation of
16 viral seeds. Examples include HuT78 cells derived
17 from a human T cell lymphoma, HeLa cells derived from
18 a human cervical carcinoma, and C127I cells derived
19 from a mouse mammary tumor.

20 What are the characteristics of continuous
21 cells?

22 Next slide.

23 They're generally constituted of a
24 heterogeneous or nonclonal mixture of cells which have
25 a selective survival potential. They have accumulated

1 mutations during extended culture which have given
2 them this selective survival capability.
3 Consequently, they're generally aneuploid.
4 In other words, they no longer maintain a diploid
5 karyology. They are immortalized in that they
6 apparently grow forever without senescing.
7 And importantly, for this discussion, they
8 can be tumorigenic or they can remain non-tumorigenic.
9 This characteristic can depend on the passage level
10 and the number, location and types of mutations.
11 For example, VERO cells are generally not
12 tumorigenic at the passage levels used for vaccine
13 production, although they can develop this capability
14 at higher passage levels. Additionally, because these
15 lines are constituted of heterogeneous mixtures,
16 different banks of the same substrate can have
17 different characteristics.
18 For example, at the same approximate
19 passage levels, some banks may be non-tumorigenic,
20 whereas other banks may be capable of forming tumors
21 in animals. Thus, it is critical that cell banks be
22 assessed on a case by case basis by each manufacturer.
23 Next slide.
24 Transformed cell lines are those which
25 have been treated by viral infection or transfection

1 of oncogenes or viral genes, or by chemical methods
2 which result in alteration of their genotype and
3 phenotype.
4 Transformed cell lines can be tumorigenic
5 even though they're not necessarily derived from a
6 tumor. 293 cells were derived from normal tissue, but
7 were transformed with sequences from an oncogenic
8 virus.
9 Importantly, transformed cells are
10 generally transformed by a known event such as
11 infection with an oncogenic virus or treatment with
12 chemicals that result in specific kinds of mutations.
13 The mutations in these cells can potentially be
14 characterized.
15 Next slide, please.
16 In contrast, tumor derived cells are
17 directly isolated from tumors of human or animal
18 origin. Generally, the events causing the tumor to
19 form are unknown or incompletely known. Tumor derived
20 cells are generally aneuploid, or non-diploid.
21 These too can be heterogeneous. For
22 example, clones can be isolated from tumor derived
23 cell lines which have lost the tumorigenic phenotype.
24 So simply because a cell line is tumor derived does
25 not mean that it is tumorigenic.

1 These characteristics do not equate.
2 Again, tumorigenicity must be assessed on a case by
3 case basis.
4 Next slide, please.
5 The cell substrates proposed to be used to
6 produce investigational vaccines will be shown in the
7 next few slides. Investigational vaccines are
8 proposed to be made in the same cell substrates as
9 currently licensed products, as well as novel
10 substrates or novel uses of currently used substrates.
11 The Committee has received a table listing
12 the substrates used to manufacture vaccines currently
13 licensed in the U.S., to which you may wish to refer.
14 Please keep in mind that the examples I
15 will give may be either from active investigational
16 new drug applications, or INDs, or they may be from
17 products of which we are aware that are in the pre-IND
18 or preclinical stage of development.
19 In other words, they have not gone into
20 humans yet.
21 I've not listed the disease indications
22 nor manufacturers for these examples because that is
23 proprietary information which cannot be discussed in
24 an open forum such as this.
25 However, I will attempt to identify the

1 uses and will indicate the type of vaccine, be it
2 recombinant, live, attenuated or inactivated; and the
3 proposed use, whether it's therapeutic or
4 prophylactic.
5 Next slide, please.
6 Simple substrates or unicellular organisms
7 such as E-coli, salmonella typhae or BCG are proposed
8 for manufacture of recombinant vaccines either as
9 substrates for prophylactic and therapeutic vaccine
10 candidates or as live vectors for prophylactic vaccine
11 candidates.
12 Insect cell lines are also proposed for
13 use to manufacture recombinant vaccine candidates for
14 prophylaxis. Primary cells are proposed for
15 manufacture of live attenuated vaccine candidates,
16 live vectors, or recombinant subunit vaccine
17 candidates for prophylaxis and therapy.
18 Diploid cells are proposed for manufacture
19 of live attenuated prophylactic vaccines, often for
20 infant use.
21 I realize that I didn't say -- when I'm
22 referring to therapeutic indications, these are
23 therapeutic vaccines.
24 Next slide.
25 A number of continuous cells are proposed

1 for use. CHO cells and BHK-21 cells are used for
2 approved therapeutic biologicals either approved in
3 the U.S. or abroad, and are proposed for manufacture
4 of recombinant subunit or recombinant live vectored
5 vaccines for prophylaxis and therapy.
6 Madin-Darby canine kidney cells are
7 proposed to manufacture inactivated vaccines for
8 prophylaxis.
9 Next slide.
10 Importantly, among the proposed continuous
11 cell substrates for investigational vaccine candidates
12 are VERO cells. Although there is only one U.S.
13 licensed vaccine made in VERO cells, and it is an
14 inactivated vaccine, sponsors perceive VERO cells as
15 a preferred substrate.
16 They have proposed use of VERO for live
17 attenuated vaccines, both conventional and
18 recombinant, for prophylaxis often in healthy infants.
19 VERO cells have also been proposed for the manufacture
20 of live vectors for prophylaxis and therapy and
21 inactivated recombinant vaccine candidates for
22 prophylaxis.
23 The use of VERO cells for live viral
24 vaccines has a large regulatory impact in terms of the
25 number of potential products affected. This is a

1 novel use of a substrate that's used for currently
2 approved vaccine.
3 Next slide.
4 Other proposed substrates for
5 investigational vaccine candidates include virus
6 transformed cell lines to produce recombinant live
7 vectors for prophylaxis and tumor derived cell lines
8 for inactivated, live, attenuated and highly purified
9 recombinant subunits for prophylaxis and therapy.
10 Next slide.
11 Finally, tumor derived lines are proposed
12 for isolation of recombinant viral seeds for live
13 attenuated prophylactic vaccine candidates.
14 This example is important because HeLa
15 cells, which are believed to have been -- to have
16 contaminated in overgrown, early cultures of Hep2
17 cells, are known to contain human papilloma virus Type
18 16 sequences, the probable source of tumor formation.
19 However, these cells are not proximal to
20 the product. They are proposed for isolation of the
21 viral seed, which will then be propagated in a
22 continuous cell line for production.
23 Next slide.
24 Why would a sponsor propose to grow
25 viruses in novel substrates such as continuous,

1 transformed or tumor derived cell lines? Such cell
2 lines have a growth advantage almost by definition.
3 They survive better in culture than primary or diploid
4 cells.
5 They can be more readily adapted for
6 growth in large scale bioreactors or fermenters, or in
7 serum-free medium. This facilitates commercial scale
8 production. And use of serum-free medium helps
9 eliminate a potential source of adventitious agents.
10 In fact, in some cases, including the
11 example I will soon give, it may be the only feasible
12 way to achieve commercial scale production. And cell
13 lines can be engineered to produce novel products that
14 might be infeasible otherwise.
15 Also, one should consider that it is
16 possible for such substrates to be characterized,
17 unlike primary cells. Thus, it is feasible that a
18 safer product might result.
19 Next slide.
20 Additionally, often viruses can replicate
21 to significant higher titers in such substrates
22 resulting in higher yield process. This allows
23 commercial scale production and may result in a
24 cheaper product.
25 In some examples, viruses cannot replicate

1 at all in other substrates. Continuous, transformed
2 or tumor derived cell lines may be the only sensitive
3 substrate for particular viruses. In part, this may
4 be because the substrate provides necessary genes to
5 support viral replication.
6 An example of this is the adenovirus
7 vectors being studied for gene therapy. Such
8 adenovirus recombinants are defective for replication,
9 so they cannot be grown in WI38 cells as are the
10 licensed adenovirus vaccines.
11 But they do replicate in 293 cells which
12 provide the missing adenovirus genes.
13 Next slide.
14 So why are we concerned about cell
15 substrates? Well, because they are a source of
16 contamination of the products manufactured in them.
17 They can be the source of adventitious agents, the
18 source of tumorigenic potential, and the source of
19 residual cellular DNA which can have both infectivity
20 or tumorigenic potential.
21 Dr. Krause will talk later about this a
22 little more.
23 Next slide.
24 Adventitious agents are a concern for any
25 cell substrate. Earlier I described the types of

1 agents to be screened and the tests for these.
2 However, some substrates present novel concerns as
3 they may contain express viruses such as exogenous
4 oncogenic viruses or recombinant viral elements.
5 Or, the cellular DNA from the substrate
6 may be the contaminant. This DNA may contain
7 proviruses or viral genomes which could then transmit
8 infectivity.
9 Next slide.
10 Oncogenicity, or potential to cause tumors
11 in recipients, is a major concern for considering use
12 of those cells that have tumorigenic potential.
13 But what are the potential mechanisms for
14 transmitting tumorigenic potential from cell
15 substrates to final products, the viral vaccine?
16 As you heard earlier from Dr. Lewis, these
17 include the cells themselves, cellular proteins
18 including oncoproteins and growth factors,
19 adventitious oncogenic viruses, and cellular DNA.
20 I'll go into each of these in more detail.
21 Next slide.
22 Cells which have been assessed to be
23 tumorigenic in animals could quite potentially be
24 oncogenic in humans. However, even the least purified
25 viral vaccines are generally filtered to remove

1 potential bacterial contamination and cellular debris
2 from production.
3 This filtration would also remove intact
4 substrate cells. Cellular proteins might be
5 concerning, but they have no way to replicate, so they
6 would not persist in the recipient and would only be
7 able to exert briefly any possible effect before being
8 degraded in the recipient.
9 Next slide.
10 More concerning is the potential for
11 exposure to adventitious oncogenic viruses. The
12 primary reasons for this concern are that screening
13 methods for these viruses are difficult or relatively
14 insensitive, and that there may exist currently
15 unknown or occult agents that have never before been
16 detected despite use of current technology.
17 And finally, concern has centered on
18 cellular DNA which could be inserted into the cells of
19 the recipients and transmit the tumorigenic potential.
20 Cellular DNA could contain activated oncogenes, or it
21 could activate oncogenes or inactivate tumor
22 suppressor genes in the recipient by insertional
23 mutagenesis.
24 Cellular DNA could also contain the
25 proviruses or viral genomes of oncogenic viruses. The

1 methods for assessing tumorigenicity of cellular DNA
2 are problematic. Dr. Krause will discuss this further
3 later.
4 Next slide.
5 Now that I've listed a host of potential
6 problems, you might ask why anyone would consider use
7 of these substrates. Therefore, I'll give you a
8 specific example to shed light on the rationale for
9 possible use of neoplastic substrates.
10 HuT78 or similar human tumor derived or
11 virus transformed T cell lines have been considered
12 for development of traditional approach HIV vaccines;
13 in other words, live, attenuated or inactivated HIV.
14 Consequently, CBER has begun to develop
15 policy to guide sponsors in the safe development of
16 such candidate vaccines. To these ends, a workshop
17 was held in 1996 at the National Cooperative Vaccine
18 Development Groups for AIDS Annual Meeting in
19 Bethesda, Maryland.
20 This workshop helped identify issues of
21 concern. The proceedings were published in *AIDS*
22 *Research and Human Retroviruses*.
23 In addition, as you've heard from Dr.
24 Lewis, CBER is proposing to hold a future workshop to
25 discuss use of neoplastic substrates in a more global

1 manner.

2 Next slide.

3 Production of live, attenuated or

4 inactivated HIV vaccine candidates will require the

5 use of cells in which HIV can replicate.

6 Human peripheral blood mononuclear cells

7 pose problems for commercial scale production and

8 would require lot by lot screening of donors and cells

9 for adventitious agents. Lot to lot consistency may

10 also be an issue.

11 Human tumor derived or virus transformed

12 T cells support the replication of HIV, and I'll

13 discuss this more on a moment. Alternative

14 substrates, which might seem preferable, have not, to

15 date, been developed.

16 Even if such an alternative substrate were

17 engineered, it is unclear that commercial yield of HIV

18 would be obtainable or whether the receptors would

19 remain express long enough for HIV to infect and

20 replicate in such cells.

21 Next slide.

22 Human T cell lymphoma derived or virus

23 transformed T cells lines have been proposed by

24 various potential sponsors. Tumorigenicity remains a

25 concern, including the following issues: residual

1 cellular DNA and the imperfect methods available for
2 measuring tumorigenicity.
3 Inactivants in the case of inactivated
4 vaccine candidates might actually decrease or
5 eliminate tumorigenicity.
6 But there remains an unknown significance
7 for vaccines if the starting material (the cell
8 substrate), but not the final product (the vaccine),
9 has tumorigenic potential. Assays for tumorigenicity
10 of cells, DNA and the final product are problematic,
11 as will be discussed by Dr. Krause.
12 Furthermore, purification levels
13 achievable -- next slide, I'm sorry -- for a multi-
14 component virion are unlikely to be as high as those
15 for single recombinant protein. Adventitious agents
16 are, of course, a concern for every cell substrate.
17 But in the case of HuT78 cells, there is
18 a concern because these would be of human origin;
19 because tumor viruses such as HTLV1 may have caused
20 the tumor, it may be difficult to detect residual
21 sequences by current screening methods; and because
22 non-vaccine retroviruses may be present which could
23 pseudotype with the vaccine virions or recombine with
24 the vaccine provirus to form new viruses of known
25 pathogenicity.

1 Next slide.

2 Now I said I would give the specific
3 example for the purpose of demonstrating why one would
4 consider using neoplastic cells for vaccine
5 production, and thus far I've only talked about the
6 issues of concern for risk, but there is a large
7 potential for benefit.

8 As you well know, on a global basis,
9 greater than 30 million people have already been
10 infected with HIV. The epidemic is continuing to grow
11 globally with little sign of abatement anywhere.
12 Approximately 16,000 new infections occur daily.

13 And very few, if anyone, survives once
14 infected with HIV, and there remains no demonstrated
15 cure.

16 The therapies available that prolong life
17 are unaffordable for the majority of infected
18 individuals because greater than 90% of them live in
19 developing countries. Thus, a safe and efficacious
20 vaccine to prevent new infections would have a huge,
21 global, public health benefit.

22 Next slide.

23 But why try live, attenuated or
24 inactivated HIV vaccines? Well, because there are
25 only a few recombinant vaccine candidates reaching the

1 Phase III of clinical development. The Baltimore
2 Committee and others have expressed the need to
3 simulate development of more approaches to increase
4 the potential candidate pipeline.
5 Most efficacious viral vaccines are live,
6 attenuated or inactivated viruses. These approaches
7 have been proven for other viral diseases, and they
8 provide a multi-component immunogen which presents the
9 immune system with multiple targets.
10 This may be of critical importance in the
11 case such as HIV for which there remain no known
12 correlates of disease protection.
13 Next slide.
14 CBER weighs risk and benefit in the
15 evaluation of vaccines. We have begun to develop
16 policies to assess risk from tumorigenic or tumor
17 derived cell substrates in response to manufacturers'
18 requests for guidance.
19 This has included issue identification,
20 proposals for research to assess risk sources,
21 development and promulgation of test methods, and
22 establishment of criteria for acceptable levels of
23 risk which is dependent upon the intended use.
24 Next slide.
25 CBER has considered how to measure risk.

1 Ideally, a substrate should be free from viral
2 contamination; but if the substrate is contaminated,
3 then viral clearance or inactivation during production
4 processes should be validated.
5 Tumorigenic potential could be estimated
6 by measuring the quantity, integrity and state of
7 residual cellular DNA. The WHO has recently revised
8 their guideline of an upper limit of 100 picagrams of
9 cellular DNA from continuous cell lines, which was
10 based on scientific data available at that time, to
11 ten nanograms.
12 Furthermore, determining better methods to
13 measure tumorigenicity of DNA would help in risk
14 estimation. Because the cells themselves are the most
15 obvious source of tumorigenicity, as is demonstrated
16 in animals, validation of cell clearance provides a
17 measure of safety.
18 Next slide.
19 To summarize, currently CBER has no
20 specific regulation prohibiting the use of a
21 particular cell substrate for the production of viral
22 vaccines. Our regulatory authority is granted to
23 ensure product safety.
24 CBER also has a public health mission "to
25 facilitate the development of new and improved, safe

1 and efficacious vaccines." Thus, CBER must work with
2 manufacturers to provide guidance on how to meet the
3 regulations; in other words, to demonstrate product
4 safety.
5 This is a guiding principle behind the FDA
6 Modernization Act approved by Congress last year.
7 Next slide.
8 Traditional approach vaccines -- in other
9 words, live, attenuated and inactivated viral
10 preparations -- remain the most proven approaches to
11 development of efficacious vaccines. These types of
12 vaccines must be prepared in cell substrates.
13 Next slide.
14 There still exists significant public
15 health needs which encourage manufacturers to consider
16 novel and potentially more problematic product
17 approaches because, for one thing, the easy things
18 have been done already; and as old disease are
19 controlled, like smallpox, polio and measles, other
20 existing diseases gain in importance to be conquered.
21 And as HIV and other emergent diseases
22 have taught us, new diseases do arise. Many of these
23 emergent diseases, like HIV, are not simple to
24 conquer.
25 This concludes my presentation. I was

1 going to introduce the next speaker at this point; but
2 I understand that we're going to have a break now, so
3 I'll finish here.
4 CHAIRPERSON FERRIERI: Thank you, Dr.
5 Sheets.
6 I think we'll keep the questions for a
7 later period. And we will go into our scheduled
8 break. We will resume promptly at 10:25.
9 (Whereupon, the foregoing matter went off
10 the record at 10:07 a.m. and went back on
11 the record at 10:25 a.m.)
12 CHAIRPERSON FERRIERI: Could we all
13 assemble now, and the Committee members and other
14 invited guests please come to the table? We've had a
15 nice, long break now of almost 25 minutes.
16 We'll move into the rest of the session,
17 if you could please take your seats.
18 We're going to keep to the schedule, and
19 questions then can be held for the -- after the two
20 presentations. I think that will work best, and
21 everyone can judge what the priorities are.
22 For those of you who are celebrating
23 today's National Smoke Out, I want to encourage you to
24 stay with it. I know what it's like, and certainly
25 congratulate any of you who have decided to do that

1 today.

2 If we keep the breaks too long, then you

3 might crave cigarettes more, so we'll try to restrain

4 ourselves.

5 The next talk is experience with

6 therapeutics derived from mammalian cells, and Dr.

7 Kathleen Clouse from the Office of Therapeutics, FDA,

8 will speak.

9 I'm sorry if I didn't pronounce your name

10 correctly, Dr. Clouse.

11 DR. CLOUSE: I'm Dr. Kathleen Clouse from

12 the Division of Cytokine Biology in the Office of

13 Therapeutics Research and Review.

14 Within the past 20 years, the

15 biotechnology industry has developed a wide range of

16 products for many subacute, acute and often life

17 threatening indications.

18 Over 40 safe and effective products have

19 been licensed by the Center For Biologics Evaluation

20 and Research, and many of these have been derived from

21 neoplastic cell substrates. The success of these

22 biologics has been achieved, in part, due to efforts

23 taken to assure product safety.

24 I have been invited to speak to you today

25 about our experiences and practices in the Office of

1 Therapeutics Research and Review in dealing with
2 safety issues concerning recombinant therapeutic
3 products that are derived from mammalian cell lines.
4 Now, aspects of my talk are also
5 applicable to issues concerning recombinant subunit
6 vaccines, but differ significantly from issues that
7 are pertinent to live, attenuated or inactivated
8 vaccines.
9 As shown here, there are major differences
10 between licensed CBER vaccine and therapeutic biologic
11 products. First of all, the intended use. For
12 vaccines, it's for prophylaxis, obviously; whereas,
13 for therapeutics, it's been used for treatment of
14 often very acutely ill people.
15 So the patient population in general for
16 vaccines is healthy, versus ill for therapeutics.
17 The dosage schedule and route of
18 administration can differ. For whole vaccines, you
19 would dose, in many cases, based on infectious units.
20 For biologic therapeutics, you would dose based on
21 units of biological activity in some cases and, in
22 other cases, based on mass.
23 And the dosage can get as high as
24 milligram quantities.
25 The schedule also differs. In vaccines,

1 you give them for a very short period of time with
2 long term effects; whereas, with therapeutics,
3 although initially they were used for short term
4 treatments in acutely ill patients, we're now starting
5 to treat more chronically ill patients on a long term
6 basis.

7 The routes of administration differ for
8 both vaccines and therapeutics. Now non-recombinant
9 vaccines cannot achieve the same level of product
10 purity that is achievable with recombinant
11 therapeutics or subunit vaccines, and that is because
12 you're dealing, in general, with one single purified
13 protein for your recombinant therapeutics.

14 Now the licensed recombinant products
15 within the Office of Therapeutics have been expressed
16 in the following substrates: nine products have been
17 licensed that are expressed in E-coli, two from yeast;
18 but the need for more complex protein processing has
19 resulted in the use of mammalian cell substrates.

20 And what we find is there are actually 18
21 products that have been licensed from mammalian cell
22 lines, but these are pretty much limited to two cell
23 lines at this point: CHO cells, Chinese hamster ovary
24 cells; and the SP20 murine myeloma cell line.

25 Now, 11 of the 18 products have been

1 expressed in CHO cells and seven in the SP20, or
2 subclone, cells.
3 Now, this reflects a common practice in
4 industry that, once something has been licensed
5 successfully using a particular cell substrate, the
6 inclination is to continue to use it because more and
7 more knowledge has been accumulated regarding the safe
8 use of these cell lines.
9 However, there are situations that arise
10 when certain products are not amenable to expression
11 in the existing cell lines. And this leads to
12 scientists going to different cell substrates, and
13 then needing to provide more documentation to the
14 agency regarding the safe use of these substrates.
15 Now the licensed therapeutics that have
16 been derived from mammalian cells to date include
17 tissue plant plasminogen activator, or Alteplase;
18 erythropoietin; DNAse, which is marketed as Dornase
19 Alpha; interferon beta 1A, or Avenex; and, more
20 recently, a fusion protein that consists of the Fc
21 portion of human IgG1 and the (p75) TNF receptor which
22 is marketed as Enbro; and we have 13 monoclonal
23 antibodies.
24 Of the monoclonal antibodies, about seven
25 have been expressed in the SP20, but at least six have

1 been expressed in CHO cell lines.

2 Now the documents available through CBER
3 concerning cell substrate use include the ICH guidance
4 document on cell substrates and the "Points To
5 Consider" document that were referenced by Dr. Sheets.

6 But, in addition, there's a "Points To
7 Consider" document that came out in 1997 regarding the
8 manufacture and testing of monoclonal antibody
9 products. And most importantly, from my talk, is an
10 ICH guidance document on viral safety evaluation of
11 biotechnology products that are derived from cell
12 lines of human or animal origin.

13 This guidance document pertains to
14 recombinant biologic therapeutics and also is
15 applicable to recombinant subunit vaccines, but does
16 not apply to whole vaccines or gene therapies.

17 Now, the current approach to working with
18 cell lines to produce biological therapeutic products
19 focuses on production, identification and
20 characterization of the cell substrate; but also on
21 validation of the manufacturing process for removal or
22 inactivation of adventitious agents, and also testing
23 of the bulk drug substance in the final finished drug
24 product to assure safety for the patient.

25 Characterization of the cell lines

1 intended for use in the manufacture of biologics
2 includes documenting the history and general
3 characteristics of the cell line, establishing a cell
4 banking system consisting of a master cell bank and
5 working cell bank, and implementation of quality
6 control testing.
7 Now, the same regulations apply to
8 therapeutics as to vaccines, and these were discussed
9 in detail by Dr. Sheets, so I will not go into them
10 again.
11 But, in addition to characterization of
12 the host cells with regard to the cell substrate
13 issues, their source (phenotype and genotype),
14 detailed information must be provided to the agency
15 regarding the expression vector system for recombinant
16 therapeutics.
17 The source and restriction map of the gene
18 construct has to be provided. The source, origins of
19 replication, the promotors, enhancers and any
20 antibiotic resistance genes present in the vector have
21 to be identified.
22 The final gene construct, the cloning
23 process for generating it, has to be provided, the
24 information. And the cloning and actual establishment
25 of the cell line also must be provided.

1 Now, once the cell line has been cloned
2 and the master cell bank and working cell bank has
3 been generated, they are tested as described by Dr.
4 Sheets. But, in addition to testing of the master
5 cell bank and working cell bank, for therapeutics
6 there's extensive production cell testing.
7 Now, the production cells are derived from
8 -- directly from the working cell bank and, in
9 general, extensive testing is done throughout the
10 manufacturing process.
11 But at least once the production cells are
12 tested at the peak of their in vitro life span, and
13 extensive testing is done with regard to purity for
14 all of the adventitious agents described by Dr.
15 Sheets, and also for cell substrate stability.
16 And we're looking for consistent
17 production of the product throughout the life span of
18 the cells. We're also looking for retention of the
19 production capacity during long term cryopreservation
20 of these cells.
21 And also, at the peak of their production,
22 we're very interested in the genetic construct
23 stability.
24 So part of the extensive testing that is
25 done is to sequence the genetic construct that's

1 present in the master cell bank and comparing it to
2 that that's present in the production cells at the
3 peak of their in vitro life span.
4 A quality control of the cell substrates
5 that are used for production includes cell culture
6 media where you monitor additives derived from animal
7 sources, any antibiotics, growth factors and so on;
8 and again, emphasizing management of the cell
9 cultures, looking for product consistency and constant
10 adventitious agent testing; and also specific testing
11 on the unprocessed bulk drug and the processed bulk
12 drug and the final drug product.
13 The companies will set lot release
14 specifications for the final bulk drug substance and
15 drug product, and they will also set specifications
16 for parameters to monitor in vitro production and
17 management of the cell cultures.
18 The quality control testing for biologics
19 again includes testing for bacteria and fungi,
20 mycoplasma, viruses, both adventitious -- and one
21 that's omitted from there -- and also endogenous
22 retroviruses.
23 Tumorigenicity testing is actually not
24 required for the therapeutic products licensed to date
25 because it's not required for continuous cell lines

1 derived from rodents since they've already been proven
2 to be tumorigenic.
3 However, I would like to emphasize
4 addition practices that are employed for -- with
5 regard to virus monitoring and to reduce -- that are
6 geared at reducing the risk of virus contamination in
7 biologic products.
8 And this is the concept of viral
9 validation. Now, the risk of viral contamination is
10 a feature that's common for biologic products that are
11 derived from cell lines. And as mentioned before, the
12 contamination can come endogenously from cell
13 substrates that express virus particles, and you can
14 have contamination from adventitious virus.
15 And the concern, obviously, is that these
16 infectious agents could be transmitted to patients and
17 could be infectious for the patient.
18 So there are three complimentary
19 approaches that therapeutics uses for the control of
20 potential viral contamination. First of all is to
21 select and test the cell lines and raw materials for
22 the absence of viruses.
23 And again, this was dealt with in detail
24 by Dr. Sheets. Secondly, to assess the capacity of
25 the production process to actually clear infectious

1 viruses should a contaminant be introduced that you do
2 not pick up on.
3 And also to test the product at
4 appropriate production steps again for the absence of
5 adventitious virus.
6 Now, no single approach will necessarily
7 establish the safety of a product. First of all,
8 there's an inherent limitation to quantitative viral
9 assays that are used in that their ability to detect
10 low viral levels pretty much depends on the size of
11 the sample.
12 So the confidence that virus is absent
13 from a product may not really result from direct virus
14 testing. However, you can achieve a certain level of
15 confidence by showing that the purification process
16 itself can remove or inactivate viruses.
17 So the type and extent of viral tests and
18 viral clearance studies in general will depend on the
19 extent of the cell bank characterization and
20 qualification that was done, the nature of any viruses
21 that were detected in this characterization, the
22 culture methods that are used for product production
23 and all of the media components that are used, the
24 results of viral testing after cell culture, and
25 again, the ability of the process to clear the

1 viruses.

2 Now, validation of viral elimination

3 requires the following:

4 First, you have to select appropriate

5 viruses for the testing. The manufacturer has to

6 prepare a scaled down manufacturing system. They have

7 to do an analysis of step-wise virus elimination.

8 They have to determine whether virus

9 elimination is due to physical removal of viruses or

10 inactivation of viruses. If inactivation of virus is

11 one of the steps, then kinetics of inactivation have

12 to be determined.

13 And then, at the end, the manufacturer has

14 to estimate the overall combined effect to generate a

15 final figure for the overall viral clearance for the

16 system. In the next few steps I'll discuss each of

17 these individually.

18 As far as the viruses used for viral

19 clearance studies, first of all, they should resemble

20 viruses that could contaminate the product. And they

21 also should represent a wide range of physicochemical

22 properties so that you can adequately assess the

23 ability of the system to remove any potential viral

24 contaminant.

25 They should include relevant viruses. And

1 by this, these are viruses that are either identical
2 to or are the same species of viruses that can
3 contaminate the cell substrate and have been
4 identified as contaminants.
5 For specific model viruses -- and these
6 are viruses that are used when relevant viruses are
7 unavailable. And relevant viruses may be unavailable
8 if they either cannot be grown to a high titer or if
9 they're too infectious to be used for viral validation
10 studies.
11 And generally, the specific model viruses
12 are closely related to the known and suspected
13 viruses. They're generally in the same genus and
14 family. In addition, nonspecific model viruses should
15 be used.
16 And these viruses are used for the
17 purposes of characterizing the capacity of the
18 manufacturing system to inactivate or remove viruses
19 in general; in other words, to characterize the
20 robustness of the manufacturing processes.
21 And the nonspecific model viruses should
22 possess different properties. The properties should
23 be varying DNA and RNA genomes. You should have
24 representative viruses that are enveloped and non-
25 enveloped. They should have low to high

1 physicochemical resistances.

2 For example, resistance to acid pH is one
3 parameter. They should range in size. Very often
4 they range from 20 nanometers to 200 nanometers. And
5 all of these should be viruses that can be grown to
6 high titers to give an adequate indication of the
7 level of virus clearance that can be achieved.

8 Now, once the viruses have been selected
9 -- and generally you select three or four model
10 viruses for each viral validation study that's done --
11 a scaled down manufacturing system should be set up
12 outside the normal manufacturing facility.

13 And this is deliberately to prevent the
14 introduction of any virus into a manufacturing
15 facility that is operating under good manufacturing
16 practices. This also enables performance of the viral
17 testing by qualified staff with virologic expertise.

18 Generally what happens is there's a
19 collaboration between the manufacturer and an outside
20 company that does viral testing. The manufacturer
21 actually provides the scaled down model system and
22 employees that actually operate this.

23 The viral testing group provides the high
24 titer virus and actually does the virus isolation and
25 testing as it goes through the manufacturing process.

1 When they generate a scaled down
2 manufacturing system, they have to validate to show
3 that they -- this adequately represents the production
4 procedures. It has to be scaled down proportionately,
5 and all of the production parameters have to be
6 duplicated, including such things as buffer flow rates
7 and so on.
8 And finally, if it's impossible to
9 identically or accurately scale down any aspect of the
10 manufacturing process, the manufacturer has to
11 determine the impact of the production deviations on
12 the viral clearance studies and how they may reflect
13 the outcome of the studies.
14 So for analysis of step-wise virus
15 elimination, first it's desirable to assess the
16 contribution of each major production step. And
17 sufficient virus should be present in the material at
18 each step.
19 Generally we try to select a virus -- or
20 the company selects a virus that can be grown to at
21 least $10^8$ particles per ml. The virus should be added
22 to in process material at each step.
23 Generally what's done is the manufacturer
24 provides virus -- or the manufacturer provides drug
25 substance from at least three lots of material at

1 various steps in the production.

2 And from this, when the material has been

3 run through the purification process, quantitative

4 infectivity assays should be done. And these should

5 be shown to have adequate sensitivity and

6 reproduceability.

7 Now, it is important -- because virus

8 elimination can consist of physical removal versus

9 inactivation, both of these serve as a mechanism for

10 virus reduction. It's important that, if there is

11 virus elimination at any step, the mechanism of the

12 loss of viral infectivity be determined.

13 If inactivation of virus does occur, then

14 samples need to be taken at different times and an

15 inactivation curve should be constructed so that the

16 kinetics of virus inactivation can be determined.

17 And the purpose of this is to make sure

18 that all of the parameters are in place to make sure

19 that the product is exposed to the appropriate

20 conditions so that any virus that's present would be

21 inactivated.

22 Now, in order to determine the overall

23 viral clearance, statistical analysis has to be used

24 on the data, and the results should be statistically

25 valid to support the conclusions that are drawn. And

1 the statistics that should be used are described in
2 Appendix 3 of the ICH viral validation document.
3 So, in order to estimate the combined
4 effects of the viral inactivation and clearance, they
5 need to quantitatively estimate the overall level of
6 virus reduction that's achieved. And it's important
7 that they show that there is an excess capacity for
8 viral clearance within the system.
9 So this means that they have to compare
10 the amount of virus that's eliminated to the amount of
11 virus that's present, let's say, in the unprocessed
12 bulk drug substance.
13 For murine cell lines, since there are
14 frequently endogenous retrovirus particles, this
15 amounts to processing portions of the bulk drug
16 substance and using transmission electron microscopy
17 to determine the viral burden.
18 Now, this only applies to endogenous
19 viruses. If there are adventitious viruses present,
20 you don't proceed and process the bulk drug substance
21 into final drug product.
22 From this, they need to calculate the
23 estimated number of virus particles per dose, and
24 that's described in Appendix 5 of the ICH document.
25 And they also need to calculate the level of virus

1 reduction, and these calculations are described in
2 Appendix 4.
3 So you can see the utility of the
4 document.
5 But there is one note that I would like to
6 make, and that is that a number of factors in the
7 design and execution of viral clearance study can
8 actually lead to an incorrect estimate of the ability
9 of the process to remove virus.
10 And these are also discussed in detail in
11 the ICH document, and you can use this to see what you
12 need to avoid.
13 Now, the process of viral validation can
14 actually be used to determine -- or used for risk
15 assessment, but that's not the intent of the document.
16 The intent was actually to enable the manufacturer to
17 provide confidence that any virus that entered the
18 product, in all likelihood, would be cleared and would
19 not appear in the final product that is released.
20 So, in addition to doing extensive viral
21 testing and validation of viral removal, we also have
22 to validate removal of the cell substrate. First of
23 all, they have to document removal of all the media
24 components.
25 If fetal bovine serum is used, for

1 example, in general the companies will monitor bovine
2 IgG and bovine serum albumin levels to make sure that,
3 in the final product, these are virtually undetectable
4 or at extremely low, non-immunogenic levels.
5 The same is true for any growth factors or
6 antibiotics or inducing agents that are present in the
7 media. You also have to look for removal of cell
8 derived proteins.
9 And this is done, in general, by
10 establishing a host cell protein assay where a
11 manufacturer takes non-transfected cells, prepares a
12 mock antigen, and immunizes animals, generates an
13 antibody, and sets up an ELISA that's capable of
14 detecting host cell proteins.
15 And for this, they will set lot release
16 specifications and monitor each lot of product that's
17 produced. But in addition, they have to control for
18 host cell proteins that may not be picked up in this
19 assay, but may co-purify with the recombinant product.
20 And to do that, what's frequently done is
21 they will run an SDS polyacrylamide gel and use silver
22 stain and identify all of the bands that appear in the
23 silver stained gel. They look for primary product
24 band, they look for breakdown products, and they look
25 for aggregates of the product.

1 If there are other major bands that cannot
2 be attributed to the product that is desired, they
3 have gone to great lengths to identify this, even so
4 much as eluting the protein and sequencing it to
5 identify it.
6 If it is a frequent contaminant that co-
7 purifies, then specifications have to be set for
8 release to make sure that this protein is present in
9 low levels or, alternatively, an added step in the
10 manufacturing process to remove this particular
11 protein.
12 And finally, they have to monitor for
13 removal of host cell DNA. We previously had set
14 limits of less than ten picagrams, but in most of the
15 guidance documents the requirement has been removed
16 because it does vary somewhat depending on the nature
17 of the product that is being manufactured.
18 So finally, what we can conclude is that,
19 in the 12 years using licensed biologics and in the
20 years preceding that, during their development as
21 investigational new drugs, no cell line derived
22 biological therapeutic product has been implicated in
23 the transmission of viruses.
24 Also, there is no known adverse events
25 that have occurred that can be attributed to cell

1 substrate exposure; however, this is very difficult to
2 determine.
3 Also, what I wanted to emphasize and what
4 we hope to gain from this advisory committee meeting
5 is that the complexity of cell substrate issues is
6 increasing in biologic therapeutics, and the issues
7 are also paralleling the complexity of the vaccine
8 cell substrate issues as we enter into gene therapies
9 and the proposed use of therapeutic vaccines to
10 regulate immune responses.
11 CHAIRPERSON FERRIERI: Thank you, Dr.
12 Clouse.
13 We're going to move on to the next
14 speaker. And then, following Dr. Krause's talk, we
15 will have a little time to ask questions of the three
16 preceding speakers.
17 This talk is studies on safety of cell
18 lines.
19 And if Drs. Sheets and Clouse could be
20 available close to a microphone so that, when we get
21 to the questioning period, that you would be readily
22 available.
23 MS. CHERRY: We can -- if you can find a
24 seat at the table when we get to the questions.
25 CHAIRPERSON FERRIERI: There are also a

1 lot of seats here in the front row, and there are two
2 tall microphones.

3 DR. KRAUSE: The goal of this talk is to
4 discuss our initial approach to thinking about how to
5 apply laboratory data to the assessment of cell
6 substrate risk.

7 And before I get started, I'd like to give
8 credit to Anamaria Serig-Honigman, who is a post
9 doctoral fellow in my laboratory who performed the
10 experiments I'm going to show you from my lab; as well
11 as to Keith Peden in the Laboratory of Retrovirus
12 Research whose help in formulating this talk was
13 indispensable.

14 We would like to develop a quantitative
15 approach that enables us to use laboratory data to
16 assess risks associated with cell substrates. The
17 change in precedent against the use of neoplastic
18 cells as vaccine substrates needs to be based on
19 objective scientific data that can be used to evaluate
20 levels of risk.

21 As Dr. Lewis pointed out, this could be
22 implemented by quantitatively assessing the level of
23 risk posed by each issue, establishing the probability
24 of a worst case scenario for each issue, using data to
25 evaluate the risks individually and cumulatively, and

1 using the data then to assess the relative risk of the
2 product.
3 In considering the laboratory evaluation
4 of cell substrate safety, the first question is, what
5 materials need to be tested, and by whom? Both
6 manufacturers and CBER will have to perform tests on
7 novel cell substrates and products.
8 Some of these tests may need to be
9 performed on each lot of product. Additional
10 laboratory studies to answer more general questions
11 will also need to be done. Because these studies will
12 provide general information, they should be performed
13 by public institutions.
14 It is very important that information
15 relevant to safety issues be viewed as objectively
16 obtained and readily available to all. Any product
17 produced in these novel cell substrates will need to
18 be tested extensively for the presence of adventitious
19 agents.
20 While the focus of our discussion today is
21 neoplastic cells, it should be noted that equal or
22 greater concerns related to adventitious agents may be
23 raised regarding novel primary cell substrates.
24 Testing for adventitious agents in novel
25 cell substrates includes the tissue culture and animal

1 tests that Dr. Sheets described. In many cases, it
2 may also be necessary to develop new, specific tests
3 for other agents.
4 For example, over the last years, CBER
5 developed tests for SIV, HIV and SV40 which were
6 applied to polio vaccines grown in primary monkey
7 cells in order to help address concerns that this
8 vaccine might be contaminated with those viruses.
9 This is an example of a PCR test that we
10 developed in my laboratory to detect SV40 in vaccines.
11 As you can see from the right-hand panel, this test is
12 capable of detecting between one and ten copies of
13 SV40 DNA in a vaccine sample.
14 The left-hand panel shows four samples,
15 marked one through four, in which SV40 was not
16 detected. The lanes marked V represent negative
17 controls which were performed in every other sample.
18 We tested 60 lots of OPV using this
19 method, all of which were negative for SV40. Phil
20 Minor, at the NIBSC in Britain, has also performed
21 extensive testing of polio vaccines using PCR-based
22 methods and also found the polio vaccines used in the
23 UK to be free of SV40.
24 An obvious approach to ensuring the
25 freedom of viral vaccines from adventitious agents is

1 based on the validation of viral clearance, as
2 described by Dr. Clouse. This assumes that measures
3 that could clear adventitious viruses are taken.
4 While these methods work for highly
5 purified products, they are very difficult to
6 implement for live virus vaccines for which attempts
7 at purification may affect the viability of the
8 product.
9 One area in which further research might
10 improve our ability to detect adventitious agents in
11 cell substrates is the development and implementation
12 of nonspecific assays to detect unknown viruses. In
13 implementing such assays, it's important to understand
14 the sensitivity with which they rule out the presence
15 of potential adventitious viruses.
16 One example of a nonspecific assay is the
17 polymerase chain reaction based reverse transcriptase
18 assay, or PERT, which can detect all retroviruses,
19 including those that have not yet been discovered.
20 This assay may also be combined with tissue culture
21 methods.
22 Currently performed tissue culture assays
23 are, in general, nonspecific. It is possible that
24 broadened tissue culture assays may provide better
25 sensitivity to detect adventitious agents in novel

1 cell substrates, or that improved animal models -- for
2 example, incorporating the use of immunocompromised
3 animals -- might improve the sensitivity of such
4 testing in a nonspecific way.
5 We are also interested in considering
6 nonspecific molecular assays for detection of
7 adventitious agents in cell substrates. Examples of
8 nonspecific molecular tests that could detect unknown
9 viruses are shown on this slide.
10 One approach is to use degenerate primers
11 specific for various viral species. For example, in
12 each of the past few years, new herpes viruses have
13 been discovered using degenerate PCR primers derived
14 from herpes virus polymerase sequences.
15 Another approach is to use PCR-based
16 subtraction methods such as those that have been used
17 to find viral sequences in diseased human tissues to
18 examine vaccine or cell substrate samples for the
19 presence of nucleic acids that could represent
20 adventitious viruses.
21 A third approach is to purify nuclease
22 resistent nucleic acids from a vaccine or cell
23 substrate sample and use generic primers to non-
24 specifically amplify those nucleic acids that are
25 resistant to nuclease digestion.

1 The protein capsids of many viruses
2 protect their nucleic acids from such digestion, so
3 that this method might be able to identify
4 contaminating encapsidated nucleic acids.
5 For any of these methods, it would be
6 important to understand the sensitivity to detect
7 known viruses before their ability to detect unknown
8 viruses can be evaluated.
9 According to the recently revised WHO
10 requirements for the use of animal cells as in vitro
11 substrates for the production of biologicals, the
12 amount of cellular DNA in biological products should
13 be limited to ten nanograms per dose, an increase from
14 100 picagrams per dose.
15 This limit is meant to apply to continuous
16 cell lines and not to products given orally or
17 products derived from microbial, diploid or primary
18 cell culture systems. The ten nanogram figure was
19 derived by considering data in theoretical
20 calculations regarding the tumorigenicity of injected
21 DNA.
22 However, it should be noted that, for live
23 viral vaccines in other less highly purified products,
24 it may not be possible to limit the total amount of
25 DNA to ten nanograms. While CBER is attentive to WHO

1 guidelines, CBER evaluates products on a case by case
2 basis in determining appropriate limits for cell
3 substrate DNA.
4 Thus, the question is raised, what data
5 would be required to provide assurances regarding safe
6 quantities of residual cellular DNA for vaccines
7 produced in these novel cell substrates?
8 Potential tumorigenicity of DNA from cell
9 substrates is one factor that has limited the quantity
10 of DNA in biological products. Although cellular DNA
11 from neoplastic cells has never been shown to be
12 tumorigenic in animal models, injected intact tumor
13 cells may be tumorigenic in animal models and in
14 humans.
15 Of course, some DNA from these cells would
16 persist in vaccine products.
17 As you can see, the ability of different
18 types of cells to form tumors in animal models varies
19 substantially, ranging from tens of cells for
20 endometrial carcinoma to millions of cells for 293
21 cells required to induce a tumor in half of -- or in
22 nude mice.
23 The TPD50 represents the dose of cells
24 required to induce a tumor in half of the injected
25 animals.

1 One question that CBER will need to answer
2 is whether the relative tumorigenicity of the cells
3 that are used should affect CBER's assessment of the
4 risk associated with the DNA that comes from those
5 cells.
6 Another question is whether the history of
7 the cell line, or the mechanism of transformation, if
8 it is known, should influence CBER's assessment of
9 this relative risk.
10 This slide lists several additional
11 approaches that might be used to better understand the
12 potential tumorigenicity of residual DNA from
13 neoplastic cells.
14 These include the identification and
15 validation of improved animal models for
16 tumorigenicity testing -- for example, highly
17 immunosuppressed animals or transgenic mice that are
18 deficient in p53 or the constitutively expressed
19 oncogenes such as RAS.
20 At this point, it is not clear whether
21 such models would detect oncogenic DNA with greater
22 sensitivity than other animal models. Further
23 investigation of tissue culture transformation assays,
24 like NIH 3T3 cells, either alone or in combination
25 with animal models in which transformed cells are

1 injected into animals to look for tumors, might be
2 another useful approach.
3 One could also consider assessing the
4 tumorigenicity or infectivity of cell substrate
5 extracts which could detect occult, known tumor
6 viruses. These methods could be developed in a
7 quantitative fashion for optimal use in risk
8 assessment.
9 Another issue associated with cell
10 substrate DNA that has not been discussed as
11 thoroughly as the tumorigenicity risk is the potential
12 for this DNA to be infectious. Viral genomic DNA is
13 infectious when it is injected into animals.
14 Moreover, tumor cells and primary cells
15 may harbor latent viruses and thus contain viral
16 genomes. And DNA used from cells used to produce
17 retroviral vaccines are a special case because they
18 may contain retrovirus genomes for that reason as a
19 byproduct of vaccine production.
20 Several factors may influence the
21 assessment of the tumorigenicity and infectivity risk
22 associated with residual DNA.
23 These include the total quantity of DNA in
24 the vaccine; the number of doses to be given; the size
25 of the DNA, where larger DNAs might not get into cells

1 as well and smaller DNAs might be small enough to
2 interrupt or not to encode intact genes; sequence-
3 related properties of the DNA (for example, whether it
4 encodes a virus or not); the number of copies of
5 potentially infectious or tumorigenic sequences per
6 cell; and the state of the DNA.

7 The state of the DNA includes such factors
8 as whether it is associated with chromatin, whether it
9 is integrated into a cellular genome, whether it is
10 linearized or circular, etc.

11 For the considerations raised on this
12 slide, although it is likely that they all have an
13 effect on the infectivity or tumorigenicity of
14 residual DNA in a vaccine, these studies have not, in
15 general, yet been performed in a quantitative fashion
16 that would permit us to apply a quantitative risk
17 assessment model.

18 This slide summarizes data taken from the
19 scientific literature regarding the infectivity and
20 tumorigenicity of viral DNA for several different
21 viruses when injected into several different animal
22 models.

23 And there's one mistake on this slide.
24 For polyoma virus, when the TPD50 was calculated,
25 hamsters were used and that's not written on this

1 slide -- baby hamsters.

2 Using the approach outlined in the
3 manuscript that is in your background package, on the
4 right-hand side of the table I have calculated the
5 theoretical risk associated with a product that
6 contains one microgram of cellular DNA that contains
7 a single viral genome per cell.

8 This calculation accounts for the dilution
9 of the viral genome in the cellular genome and assumes
10 that viral genomic DNA is as infectious or tumorigenic
11 when incorporated in cell substrate DNA as it is when
12 it is linearized and injected directly.

13 This risk estimation also assumes the
14 total risk is directly proportional to the amount of
15 DNA injected. The estimated risk of an infection
16 associated with this theoretical product thus would
17 range from as high as one in 8,000 for polyoma virus
18 DNA to one in tens of millions for other DNAs.

19 An improved understanding of the relative
20 infectivity of different types of DNAs might assist in
21 developing tests to ensure that dangerous quantities
22 of infectious DNAs are not in biological products
23 produced in novel cell substrates.

24 One other comparison may be useful. For
25 example, for polyoma virus DNA, it appears that this

1 DNA is quite a bit more infectious that it is
2 tumorigenic.

3 This suggests that much of our effort in
4 understanding the risk associated with DNA and
5 biological products should be focused on understanding
6 and minimizing the risk of infectivity.

7 It should be pointed out that direct
8 assessment of the tumorigenicity and infectivity of
9 residual DNA associated with a particular product may
10 be impractical. This is because, in order to achieve
11 meaningful safety margins, very large quantities of
12 DNA would need to be purified and tested in multiple
13 animal models for infectivity and tumorigenicity.

14 In the example on this slide, if a dose of
15 a product contained one microgram of residual cellular
16 DNA, assessment of a million doses in a single type of
17 assay would require testing of one gram of DNA.
18 Moreover, this approach may require use of more
19 animals than is practical.

20 That is why I believe it is important to
21 take a more general approach and understand the
22 potential underlying infectivity and tumorigenicity of
23 the different types of DNA.

24 A third concern regarding the manufacture
25 of viral vaccines in novel cell substrates is the

1 possibility that the vaccine virus might package
2 components of the substrate cells. This includes the
3 potential for packaging cellular DNA, recombining with
4 endogenous sequences, or pseudotyping endogenous viral
5 sequences.

6 A full assessment of this risk may require
7 additional experimentation designed to understand the
8 rates at which these sorts of events occur in the
9 absence of selective pressures.

10 One approach is to quantitatively assess
11 recombination or packaging rates using -- by examining
12 the packaging of reporter genes, such as antibiotic
13 resistent genes that are expressed within a sample
14 cell substrate.

15 Another approach is to directly quantify
16 cellular DNA that may be packaged within viral
17 particles.

18 The latter approach is illustrated by this
19 experiment from my laboratory in which we examined the
20 ability of herpes simplex virus to package the
21 cellular DNA of HeLa cells, which are a cervical
22 carcinoma line which contain about 50 copies of the
23 human papilloma virus Type 16 genome per cell.

24 We performed polymerase chain reaction of
25 nuclease resistent viral DNA representing the contents

1 of viral capsids to detect HPV sequences. When HSV
2 was grown in HeLa cells, we detected HPV sequences
3 associated with the HSV capsids.
4 Our negative control was HSV grown in VERO
5 cells, which do not contain HPV DNA, that was then
6 added to uninfected HeLa cells. The negative control
7 demonstrates that the HPV DNA we detected was not
8 simply a contaminant during the process of purifying
9 the viral capsids from the HeLa cells.
10 Further experiments to define the quantity
11 of cellular DNA that is packaged per virion could be
12 performed using this system. Similar quantitative
13 approaches could assess other types of viral packaging
14 of cellular components at potential recombination
15 rates between the vaccine viruses and endogenous
16 sequences.
17 In summary, I've tried to outline
18 laboratory approaches that could be used to better
19 assess safety issues associated with novel cell
20 substrates, including neoplastic cells.
21 These include extensive testing for
22 relevant potential adventitious agents, development
23 and implementation of improved nonspecific methods to
24 detect new adventitious agents with non-sensitivity,
25 the use of quantitative approaches to assessing DNA

1 infectivity and tumorigenicity, and the assessment of
2 viral -- rates of viral packaging or recombination
3 with pseudotyping of cellular sequences.
4 In addition, quantitative risk assessments
5 could and should be performed along similar lines for
6 other issues as required.
7 Thank you.
8 CHAIRPERSON FERRIERI: Thank you, Dr.
9 Krause. If you could stay at the microphone for a
10 minute or so.
11 We'll take questions from the panel that
12 are related to his presentation for information.
13 Yes, Dr. Greenberg.
14 DR. GREENBERG: Thanks for that very nice
15 presentation.
16 You've outlined a program that requires a
17 lot of laboratory experimentation to go forward. At
18 previous meetings of this Committee, we've been
19 informed about lack of funds to do experimental work,
20 and I just wonder where all of this work to define how
21 to define risk is going to happen?
22 DR. KRAUSE: That's an excellent question.
23 As you know, the amount of research resources that
24 CBER has to perform studies like this is greatly
25 limited and has become increasingly limited from year

1 to year.

2 I think that a lot of the reason that I am
3 presenting these kinds of studies to your group is to
4 get a sense from this Advisory Committee of the
5 relative importance of doing these kinds of studies in
6 coming to decisions regarding whether or not to use
7 novel kinds of cell substrates so that then
8 appropriate cases can be made to have these kinds of
9 studies done in one place or another.

10 DR. GREENBERG: Can I just ask a follow
11 up? Are manufacturers themselves investing in trying
12 to do this type of work as to form the basis of moving
13 forward?

14 DR. KRAUSE: To my knowledge, this general
15 kind of work is not being done by manufacturers. On
16 one of my earlier slides, I pointed out that I think
17 it's important for these kinds of studies to be done
18 in public institutions where nobody will suspect the
19 objectivity of the research and where one can be
20 certain that all of the work is in the public domain.

21 So that if one manufacturer does studies,
22 the question then becomes what's the motivation for
23 that manufacturer to provide that information to
24 assist another manufacturer in getting a competing
25 product approved.

1 So the answer is, to my knowledge, these
2 kinds of more general studies are not being done by
3 manufacturers.
4 CHAIRPERSON FERRIERI: Yes.
5 DR. HALL: Caroline Hall.
6 This is fascinating talks and excellent,
7 and I'm amazed at the amount of effort and work that
8 has gone into this.
9 Is it all right to go ahead?
10 CHAIRPERSON FERRIERI: Yes, we're
11 beckoning to one of the other members of the
12 Committee.
13 Sorry, Caroline.
14 DR. HALL: No, that's all right.
15 But I'm also concerned that, in this --
16 sort of as I listen to this, this mire of conundrums
17 of how you're ever going to put all these potential
18 risk factors in to have a priority of risk or set up
19 these standards -- that, in doing this, are we using
20 other standards that are, in actuality, assumptions?
21 And this is what I mean by this, is that
22 we have assumed that such things as the route of
23 inoculation -- that there are certain risks factors;
24 that systemic may be more dangerous, say, than orally,
25 etc.; that more -- a greater inoculation dose or

1 repetitive dose may be more dangerous when, in
2 actuality, could it be an individual circumstances
3 that a greater antigenic boost is actually safer.
4 Or that the inactivation procedure is
5 good, it gets rid of the adventitious agent or
6 inactivates it, but that the process may actually be
7 worse than the adventitious agent, etc.
8 So that what I'm asking is, in some of
9 these sort of -- what I think are basic standards that
10 we utilize, are they being also put in potential
11 standards and considered in the individual cases?
12 DR. KRAUSE: I agree with you completely
13 that they should be, and that, in many cases, of
14 course, you can't address those kinds of questions
15 directly. On the other hand, many of those kinds of
16 research questions can be addressed in animal models.
17 And I guess, again, that's one of the
18 reasons that we're here today is to get an assessment
19 from you, as the Advisory Committee, about what kinds
20 of information one really should have in order to
21 proceed, from my perspective, not only with tumor
22 cells or with neoplastic cells, but also with other
23 novel cell substrates.
24 But, in any event, since neoplastic cells
25 are the focus of the discussion today, to make that

1 big step.

2 DR. HALL: The assumption is they're

3 worse.

4 CHAIRPERSON FERRIERI: We won't preempt

5 that part of the morning program that Dr. Lewis will

6 be presenting to us, so we will confine the questions

7 and comments then to information.

8 Dr. Snider.

9 DR. SNIDER: Thank you.

10 I add my comments of congratulations and

11 appreciation for the quality of the presentations

12 today.

13 With regard to tumorigenicity, one thing

14 that is not clear to me about what CBER proposes to do

15 is whether investigating the mechanism would be a part

16 of what CBER would propose to do or would this be done

17 elsewhere?

18 It seemed to me, when the issue was

19 discussed, that it does make a -- it may, at least, in

20 a lot of cases, be important to know the mechanism in

21 order to perform the appropriate kinds of tests.

22 So what is CBER's plans in that regard?

23 What would you like to do?

24 DR. KRAUSE: My own bias is that, at least

25 at first blush, attempting to assess the relative risk

1 of one cell versus another, that if you understand at
2 least something about the mechanism by which a cell
3 line became immortal for one cell and you understand
4 nothing about it for another cell, there's some solace
5 to be taken in that knowledge in that there might be
6 a lower relative risk for the cell lines for which you
7 have that understanding.

8 That may not always be true and, in many
9 cases, that kind of understanding is illusory. I
10 think that, you know, understanding at a basic level
11 the mechanisms by which cells become tumorigenic or
12 oncogenic is probably beyond the scope of the kinds of
13 things that CBER or perhaps even the NIH can hope to
14 understand in a very short period of time.

15 But I think that CBER will need to call in
16 all appropriate outside expertise on those kinds of
17 issues and will need to take that kind of expertise --
18 those experiments into account. And it may well be
19 that, after doing that, experiments that should be
20 done at CBER will suggest themselves.

21 CHAIRPERSON FERRIERI: Dr. Lewis, would
22 you like to add to that response? No.

23 Another point, Dr. Snider?

24 DR. SNIDER: Well, I just wanted to follow
25 up and say that I was thinking that, you know, this

1 would be a role for NIH and for academia. And
2 therefore, if that's the case, it seems to me CBER
3 might consider having another meeting to try to foster
4 the kind of research that is going to be necessary to
5 discover these mechanisms.
6 DR. KRAUSE: I'm hoping, and I think Dr.
7 Lewis is hoping as well, that that would be one of the
8 outcomes of the public discussion of these issues.
9 CHAIRPERSON FERRIERI: Thank you, Dr.
10 Krause.
11 Dr. Kohl had a question for Dr. Sheets.
12 Do you still -- would you like to raise
13 that, Dr. Sheets?
14 DR. KOHL: Thank you.
15 Dr. Sheets, we talked at the break. We
16 kind of have breezed by the issue of protein problems
17 and, in particular, the question of prions. And I
18 wondered if you could address that.
19 DR. SHEETS: Yes, this is Dr. Sheets.
20 Is this on? Can you hear me? Okay.
21 I think that we are certainly not ignoring
22 the issue. This would be an issue possibly for all
23 kinds of cell substrates because the normal gene is
24 present. However, it is possible, in some of these
25 more novel substrates, that mutations could have

1 occurred.

2 It's problematic to assess this risk.
3 There aren't really good assays that are commercially
4 available or validated for assessing products. But
5 it's certainly not an issue that we're ignoring.

6 I didn't want to go into a lot of detail
7 about it in my presentation because it is such a
8 problematic issue. So Dr. Lewis did include briefly
9 that this is something we're cognizant of.

10 CHAIRPERSON FERRIERI: Any other questions
11 for Dr. Sheets?

12 Questions for Dr. Clouse, the presentation
13 on the therapeutics, experience with therapeutics?

14 Yes, Dr. Oxman.

15 DR. OXMAN: I just have a comment and a
16 question for Phil Krause following his very excellent
17 presentation.

18 I've been impressed that we're getting
19 very good at looking for agents that we can -- that we
20 know about, but I'm obviously concerned about the
21 agents that we don't know about. And you commented on
22 the use of degenerate primers as one approach to using
23 PCR for finding things we don't know the name of or
24 the gene structure of yet.

25 I wonder if you could expand on that a

1 little bit.

2 DR. KRAUSE: Well, obviously the use of
3 degenerate primers is only going to be useful for
4 identifying unknown agents that we know relatives of.

5 But if you take a family of viruses and
6 can identify conserved sequences within that family,
7 and often that turns out to be within the DNA
8 polymerase chain, which seemed to be among the best
9 conserved sequences in DNA viruses at least -- and, of
10 course, RNA viruses don't have DNA polymerases.

11 But I think that those kinds of primer
12 pairs that can detect members of a class of viruses
13 and thereby extend our ability to detect new members
14 that are somewhat related to, but different from, all
15 viruses could be extended.

16 The example that I gave in the talk was
17 that of herpes viruses where each of the last few
18 years, when I've gone to the International Herpes
19 Virus Workshop, a new herpes virus has been discovered
20 in some animal using precisely this strategy of using
21 these -- of first suspecting its existence, and
22 finding an appropriate sample.

23 And second, then using degenerate primers
24 that have been selected based on careful sequence
25 analysis of all of the known sequences of herpes

1 viruses, and then identifying them, and then
2 sequencing the span between the primers and find that,
3 in fact, it's different from any known herpes virus.
4 And then once one has a probe, you can go
5 on and do more work.
6 DR. OXMAN: That's a very fine and
7 powerful approach to members of families we know
8 about. And I just think this is one area that we need
9 to expand on a little bit, and that is the agents that
10 we don't know about yet.
11 DR. KRAUSE: Right. The two other types
12 of experiments that I described that I think have some
13 chance of identifying agents that we don't know about,
14 one of them relates to completely non-specifically
15 amplifying nuclease resistent nucleic acids.
16 Most viruses that -- have protein capsids
17 that will protect the viral nucleic acid from
18 nuclease, RNAse or DNAse digestion.
19 And the PCR methods that are now available
20 enable you to non-specifically, using random primers
21 or selected random primers or other similar such
22 methods, non-specifically amplify DNA that's in a
23 tube.
24 And we all know that, of course, also from
25 the O.J. Simpson case.

1 And so the idea of taking a cell substrate
2 or a sample in which one suspects that there's an
3 adventitious virus and then first completely
4 nucleasing it, getting rid of all the free DNA and
5 RNA, then perhaps ultracentrafuging it to purify
6 encapsidated nucleic acids, and then releasing those
7 nucleic acids and non-specifically amplifying them may
8 provide the way of identifying those kinds of things.
9 The other method, which is somewhat more
10 complicated, that I alluded to is attempting to use
11 subtractive techniques to find new viruses.
12 And again, since I'm a herpes virologist,
13 my greatest experience in this comes from the herpes
14 virus field, but the Karposi's sarcoma herpes virus
15 was discovered using a very powerful PCR-based
16 subtractive technique called representational
17 difference analysis.
18 And so the key there is finding a sample
19 that's worth subtracting from another in order to see
20 what's left over. And one approach might be to -- if
21 one is attempting to detect non-cytopathogenic
22 viruses, to inoculate a sample onto tissue culture and
23 then subtract early time points from later time points
24 to see whether any nucleic acids have amplified over
25 time.

1 Or, alternatively, if one goes back to the
2 nuclease resistent nucleic acid concept and subtracts
3 away the vaccine strain or something, then we might be
4 able to find something else that's left over.
5 So these are general concepts that I think
6 might be used. But I agree with you completely that
7 more research in this area is potentially very
8 helpful.
9 CHAIRPERSON FERRIERI: Thank you, Phil.
10 We have a question from Dr. Brieman.
11 DR. BREIMAN: And I think this question is
12 for Dr. Sheets, but I'm not totally sure.
13 In that wonderfully colorful piece that
14 you gave us from Maurice Hillemann, which was from
15 1978 and is an argument in favor of production of
16 biologics in cancer cells, he seems to make the point
17 there that the primary purpose for moving ahead with
18 these sorts of cell lines is really for developing
19 subunit vaccines.
20 And, in fact, he makes the comment that
21 "there is, to my knowledge, no present important live
22 virus vaccine need for which primary cells or diploid
23 cell strains will not provide an acceptable answer."
24 The impression that I'm getting from the
25 earlier discussion is that one of the driving forces

1 for this is the ability to produce HIV vaccines and
2 make them affordable, you know, for use in developing
3 countries and so forth.

4 So is this statement no longer applicable;
5 that one would have to move to these new sorts of cell
6 lines to develop, say, live vaccines?

7 I guess the other issue is that he goes on
8 in this piece to talk about dragon killing and kind of
9 -- it colorfully again talks about the -- you know,
10 what sorts of things one could then do if you were
11 producing a subunit vaccine, which includes all sorts
12 of inactivation measures, which again wouldn't apply
13 to, you know, a live virus vaccine.

14 I'm just wondering what's changed since
15 this?

16 DR. SHEETS: Well, certainly Dr. Hillemann
17 is quite a colorful character.

18 I think that it is true that early uses of
19 some of these types of novel substrates were for
20 recombinant purposes. Certainly that's why the
21 therapeutics field is much further ahead than we are
22 in considering the risk benefits for such things.

23 However, there are becoming more and more
24 increasing uses which I can't tell you all of the
25 specific indications, but certainly people are

1 considering using -- I believe it's in the literature
2 -- the Madin-Darby canine kidney cells, which is a
3 continuous cell line, for influenza.
4 Certainly influenza is grown in eggs. But
5 if we want to be able to break free of the
6 restrictions of -- for influenza vaccination
7 production -- vaccine production, which is very
8 complicated timing-wise -- you have to get the hens
9 produced.
10 Then the hens have to be producing the
11 eggs. Then you have to have each batch of eggs come
12 in so that you can produce a lot of vaccine. So all
13 the timing is very critical. A lot of that would be
14 alleviated with use of continuous cell line.
15 So that's one purpose. The HIV example
16 that I gave you, if you want to grow live HIV for
17 further inactivation or for a live attenuated vaccine,
18 it's most likely going to be viable to do so in a
19 tumor derived cell line.
20 Although it can be grown in primary cells,
21 it's unlikely that commercial scale yield would be
22 able to be achieved, and lot by lot testing for
23 adventitious agents would be a huge burden.
24 So I think there are multiple examples.
25 And we are certainly being approached all the time.

1 We have several applications for things, and also
2 sponsors who approach us before they submit an
3 application for advice.
4 So yes, this is changing. More and more
5 novel approaches are being tried.
6 CHAIRPERSON FERRIERI: Thank you, Becky.
7 Dr. Greenberg.
8 This is our last question, and then I'm
9 going to turn it back to Andy Lewis to present the
10 focused issues for discussion.
11 DR. GREENBERG: This is basically a
12 comment and a suggestion based on what Mike Oxman
13 mentioned.
14 I also am worried about the agents that
15 can't be -- that aren't known. And I would simply say
16 that the Defense Department and DARPA is investing
17 really very large amounts of monies for other reasons
18 in finding agents that aren't known, and that there
19 might be some partnering that FDA could use for some
20 of this very new technology to, in this case, look for
21 agents in these biologics, especially using micro
22 arrays and things like that for looking for signature
23 transcriptional responses in cells.
24 So maybe it would be good for somebody to
25 talk to DARPA.

1 CHAIRPERSON FERRIERI: Thank you, Harry.
2 We will flip that into one of the two key
3 issues. That's a very important item. We can amplify
4 on that.
5 Andy.
6 The rest of the hour now will be devoted
7 to these two focused items.
8 DR. LEWIS: We thank you for your
9 attention this morning.
10 In the presentations that we've made
11 before the Committee, we've tried to outline the
12 manner in which living tissues needed for vaccine
13 manufacture have been selected over the past 60 years.
14 Through the development of the polio
15 vaccine, the selection process was serendipitous and
16 opportunistic.
17 Following the discovery of SV40 in rhesus
18 monkey cells that were being used for vaccine
19 production in the 1950s and the development of the
20 human diploid cell strains in 1961, the selection
21 process shifted into a more deliberative phase that
22 we're acknowledging today.
23 As a result of this process, only six
24 types of cell cultures from the eukaryotic species
25 have been selected as substrates suitable for vaccine

1 manufacture.

2 Due to technological advances and new
3 disease causing microbes, once again it's necessary to
4 approach the possibility of expanding types of tissues
5 that can be used for vaccine production.

6 And once again, the question is, how to
7 proceed?

8 In a first attempt to address this
9 question this morning, we've shared with the Committee
10 our initial thoughts on how we might go forward. At
11 this stage of the process, we think it's premature to
12 ask the Committee to address questions regarding the
13 use of specific neoplastic cell lines as vaccine
14 substrates.

15 We thought it better to ask the Committee
16 to comment generally on the issues regarding the use
17 of neoplastic cells as vaccine substrates, and, within
18 the context of these deliberations, to address the two
19 items that I presented in my third slide this morning
20 and that I'm going to present again on the next slide.

21 So in this regard, we ask the Committee to
22 please comment on CBER's concept and approach to
23 evaluate neoplastic cell lines that are proposed for
24 use in vaccine manufacturing, and then consider any
25 additional items related to today's presentations or

1 to issues related to the use of vaccines manufactured
2 in neoplastic cells that the Committee finds
3 appropriate.
4 CHAIRPERSON FERRIERI: Thank you, Dr.
5 Lewis.
6 Well, let's open it up and address the
7 first question, and that is the general concept of the
8 use of neoplastic cell lines.
9 Who would like to lead off? Any
10 volunteers?
11 Great, Dr. Kim.
12 DR. KIM: Yes, this is Kwang Sik Kim.
13 My concern is that I don't think we
14 understand clearly the basis of tumorigenicity. And
15 without having a complete information and knowledge on
16 these issues, it will be very difficult to speculate
17 what is going to happen.
18 Good example is this morning we heard that
19 RT activity has been detected in chicken derived cell
20 lines. And, you know, I think that a similar kind of
21 findings will be obtained from other cell lines,
22 including tumor derived cell lines, and I don't know
23 what to do with that information.
24 CHAIRPERSON FERRIERI: Well, that occupied
25 several of our Committee meetings prior to your

1 joining us, Kwang Sik, so it threw many people into a
2 turmoil.
3 Any amplification on that point, those who
4 might share this concern at the table?
5 Yes, please, Dr. Folks.
6 DR. FOLKS: Tom Folks.
7 That's occupied a lot of our time at CDC
8 as well. And just to make a comment, and maybe it's
9 moving more to point two, but clearly I think that
10 when you introduce or you find new agents associated
11 with anything, or you iatrogenically attempt to change
12 something -- and I'll use xenotransplantation as an
13 example where we're heavily invested in that as well
14 in looking for the transmission of something new or
15 unknown, how do you go about knowing where you're
16 stepping?
17 And about the only thing -- or one of the
18 things you can do is surveillance, clinical
19 surveillance. And I haven't heard a lot about that.
20 And again, I think our purpose of this meeting is to
21 talk about substrates.
22 But clearly, as we move beyond substrates
23 and we start to think about application of the
24 substrates into humans, we want to be sure that there
25 is some type of random -- limited random surveillance,

1 clinical surveillance, that follows anything like
2 this.
3 And we've been surveying the reverse
4 transcriptase activity, associated type activity, that
5 children have been receiving over a number of years
6 with the measles, mumps, rubella vaccine that you're
7 alluding to.
8 And clearly, there are no sequences, no
9 avian leukosis virus, or EAV type sequences that we
10 can find in children post this type of vaccination.
11 Likewise, we're developing other surveillance tools
12 like Western Blot in serology to survey children, and
13 again we find no real conversion of children to these
14 chicken viruses.
15 So, you know, the concern is real. And
16 whenever you find something new -- and assuredly, as
17 Dr. Krause alluded to with representational difference
18 analysis, this is a powerful, powerful tool to find
19 new things that are going to appear in all types of
20 substrates in vaccines that we're currently using.
21 We have to be cautious as to what they
22 really mean, and surveillance may be one of the only
23 ways we can do it.
24 CHAIRPERSON FERRIERI: Let me refocus the
25 first question though, Dr. Folks. Would you care to

1 comment on CBER's current approach to evaluating these
2 neoplastic cell lines? As an opener, is it
3 reasonable? Is it, at the moment, based on the
4 technologies you're familiar with, sufficiently
5 comprehensive?
6 DR. FOLKS: Highly reasonable.
7 CHAIRPERSON FERRIERI: Highly reasonable?
8 I hope some of you will forgive me for calling upon
9 you, but I think of you as our experts for the
10 Committee.
11 Dr. Wold, would you care to address this
12 point of what your opinion is of CBER's current
13 approach to the evaluation of these cell lines?
14 DR. WOLD: Wold or Wolfe? Bill Wold.
15 The question has been raised -- if I could
16 make a comment first -- as to why bother to consider
17 cancer cell lines and other cell lines when there are
18 lines that have been worked -- that have worked well
19 in the past.
20 There are a number of reasons. First,
21 many viruses don't grow well and cannot be genetically
22 manipulated in the WI38s and cells of that nature.
23 Secondly, the new technology available has created
24 many new opportunities to develop genetically
25 engineered vaccines and recombinant vaccines.

1 And those kinds of genetic manipulations
2 have to be done in cells that are easily studied in
3 the laboratory.
4 And thirdly, I think if you considered
5 using other types of cell lines, you would engage in
6 an entirely new community of researchers interested in
7 vaccine development and biological development.
8 For example, academia, many of whom don't
9 want to become involved in this kind of research
10 because they don't have the resources, and it's just
11 too much trouble to get involved.
12 So I think if it were easier to do the
13 kinds of experiments that we can do now and we'll be
14 able to do in the future, it would be better for
15 everybody.
16 To comment specifically on the point, I
17 think the experiments outlined are very reasonable.
18 They're really taking the worst case scenario for, you
19 know, contamination of DNA, protein when there isn't
20 a great deal of evidence that there's a lot to be
21 concerned about with any of these particular concerns.
22 But, nevertheless, the kinds of
23 experiments that are proposed should be done, and I
24 think they're reasonable.
25 CHAIRPERSON FERRIERI: Dr. Blair, do you

1 have an opinion? Would you share your opinion with
2 us, please? I'm sure you must have an opinion.
3 DR. BLAIR: No, I think the -- there
4 clearly, in some cases, may be advantages to some of
5 the neoplastic cells in the sense that one can clone
6 them and characterize them to a much greater extent
7 than you can the continuous cell lines or primary
8 cells.
9 And I think that you -- that the
10 approaches that were described to test for those
11 things we know about and to test for -- you know, for
12 the limits of our detectability of some of those
13 things are the kinds of -- are the approaches that you
14 have to do.
15 I'm not sure how to test for those things
16 we don't know about and whether we already know
17 examples of everything that's out there such that, if
18 it were in one of our established lines, we would have
19 noticed it by now.
20 I don't know, but I think the approach to
21 establish the minimal limits and the limits of how
22 much of any potentially hazardous or potentially
23 hazardous material might be present in the output of
24 some of these established lines should -- is certainly
25 a worthwhile approach.

1 I don't know whether there's the
2 equivalent of an RFP within the FDA to get some of
3 this work done on the outside, but that's certainly
4 the kind of an approach that might get it done.
5 CHAIRPERSON FERRIERI: Thank you.
6 Dr. Wolfe.
7 DR. WOLFE: Assuming that the point that
8 Dr. Snider raised, which is, in every instance that
9 there's been an application, now or in the future,
10 clearly the only way to go is with human or animal
11 tumor cell lines, which may or may not be the case.
12 It may be that, in some cases, that's the
13 way to go. And other places, for economic or reasons
14 that aren't really that health related, the company
15 has chosen to go that way.
16 But assuming that, at least in some of
17 these instances, we would all agree that the way to go
18 is to use human or animal tumor cell lines, it seems
19 that the very careful approach both at the research
20 level for developing the methodology, and then, when
21 and if these are considered for human trials, the
22 research to check out from the Government's
23 standpoint, is very well thought out, but it is
24 extremely resource intensive.
25 And so I don't think we can answer the

1 first question without assurance because we're being
2 asked -- or the people on the Committee permanently --
3 I'm just here intermittently, I guess -- are being
4 asked is this okay without guarantees that there will
5 be the resources.
6 It seems that it would be better to have
7 the resources used in house -- it may be necessary to
8 augment that with RFPs or maybe convincing pieces of
9 the DOD or NIH, with its now $13 billion dollar
10 budget, to be interested in it.
11 But I think we have to get some assurance
12 that there will be the resources. Otherwise, nice
13 idea, but no implementation could be really dangerous
14 because it would -- going back to Dr. Krause's point,
15 these things are too important to be left to anything
16 other than public and publicly accountable
17 institutions.
18 And if the budgets aren't there for that,
19 they will be left to private institutions, and I would
20 not have the trust in those institutions to do the
21 very thoughtful kind of processes being described
22 there.
23 CHAIRPERSON FERRIERI: Oh, I agree with
24 you completely and think that we need considerable
25 public advocacy to see that the resources are

1 available. These are very vital.

2 I'm targeting Dr. Hughes. I wonder if

3 you'd like -- with your position as Head of the

4 Molecular Carcinogenesis Laboratory, if you would like

5 to add your perspective to question one.

6 DR. HUGHES: I'm pleased certainly by what

7 I've heard this morning. I think the approach in

8 general is thoughtful.

9 CHAIRPERSON FERRIERI: Is your microphone

10 working, Dr. Hughes?

11 DR. HUGHES: I don't know how to comment

12 on that.

13 (Laughter.)

14 CHAIRPERSON FERRIERI: We'll try to fix

15 it.

16 DR. HUGHES: I think the first thing

17 though that needs to be kept very firmly in mind if

18 one is considering neoplastic -- using neoplastic

19 cells is not the risk in the absolute sense, but, in

20 effect, the comparative risk relative to normal cells.

21 And the reason for pointing that out is

22 that, someone who fiddles around with retroviruses in

23 one form or another, I think it's only fair to point

24 out -- and I think the experience with the avian

25 system that we heard something about this morning is

1 illustrative -- that you are not going to be able to
2 avoid, even with normal cells, some potential risk.
3 I think if you're contemplating using
4 neoplastic cells, and I think that's a reasonable
5 thing to contemplate, one needs to think very
6 carefully, wherever possible, about the route by which
7 those cells became transformed.
8 And I think it's important to think
9 differently about virally transformed cells and cells
10 that are transformed by some relatively well
11 understood bits of DNA damage, loss of suppressor
12 genes or activation of some endogenous oncogene like
13 NIC.
14 And I think, as was outlined, and I think
15 nicely, one needs to think about the relative risks in
16 any derived agent-reagent, whether it comes from
17 normal cells or transformed cells, at the protein DNA
18 and viral level.
19 And certainly my prejudice, which I think
20 reflects what was discussed this morning, is that the
21 risk of protein is relatively modest. The risk of DNA
22 is less well understood, but probably also relatively
23 modest if one excludes virally transformed cells.
24 And I don't think anyone is really
25 seriously contemplating using those.

1 And the real problem is viral. But I
2 would point out, and I think this echoes a bit what
3 Don Blair said, it may, in some ways, be easier to
4 assess the contamination and the risk of viral
5 contamination with a well characterized permanent cell
6 line than it is with normal cells.
7 And I certainly think that one needs to be
8 cautious in detecting "unknown agents." But that, I
9 point out, is at least as big a problem, if not a
10 bigger problem, if one is getting, you know, eggs or
11 tissues from here, there and everywhere.
12 It's an unavoidable issue. And I think
13 the final point, which I don't believe was discussed,
14 is that maybe some thought should be given, since
15 there was discussion of HIV, to differentiating agents
16 or reagents that are intended for use in
17 immunocompromised individuals and those that are not.
18 CHAIRPERSON FERRIERI: Thank you.
19 Back to Dr. Wolfe and then Dr. Johnston.
20 DR. WOLFE: Yeah, a quick comment, which
21 was I think that your statement that you don't think
22 anyone is seriously considering using virally
23 transformed cells is not correct.
24 I think that one of the -- from the
25 discussion, as I have read it this morning, that that

1 is one of the things that's being considered.

2 And, for the same reason as you, I would

3 be concerned about that.

4 DR. HUGHES: Well, I think it's very

5 important to distinguish when one uses the term

6 virally transformed. I would not call 293 virally

7 transformed.

8 DR. WOLFE: You wouldn't?

9 DR. HUGHES: That is a virus that is

10 transformed by a modest component from adenovirus.

11 DR. WOLFE: Okay, so you --

12 DR. HUGHES: And I think that there's

13 really no reason to expect that if you -- that you

14 could resurrect an infectious agent out of a 293 cell

15 since the 293 cell does not contain the vast majority

16 of adenoviral sequences.

17 And I think that one could easily argue

18 that the only way that you're going to recover

19 something like an infectious adenovirus is to add an

20 infectious adenovirus, and I think that's a different

21 sort of situation which one should guard carefully

22 against.

23 DR. WOLFE: I thought you were talking

24 about the --

25 CHAIRPERSON FERRIERI: Thank you, Dr.

1 Hughes.

2 Dr. Sheets, do you want to add to this

3 discussion? And then we'll go back to Dr. Johnston.

4 DR. SHEETS: I did want to clarify.

5 Certainly there are people considering 293 cells for

6 the production of adenovirus recombinants.

7 The other thing is there are people

8 considering use of HeLa cells, which we're -- we are

9 presuming, because this is cervical cancer and there

10 is human papilloma virus Type 16 in there, that that

11 was the -- one of the transformation events.

12 So you shouldn't discount that these

13 aren't being considered.

14 Now, I can't comment on what the products

15 are or whether -- what the risk-benefit ratio would

16 be, how FDA is viewing such applications or potential

17 applications, but it isn't a truth to think that no

18 one out there is considering them. They certainly

19 are.

20 CHAIRPERSON FERRIERI: Dr. Hughes.

21 DR. HUGHES: It is -- you may know more

22 about this than I. When you speak of HPV being

23 present, are those -- how well characterized are the

24 genomic elements in HeLa? Are they intact? Do we

25 have whole viral information? Do we know?

1 CHAIRPERSON FERRIERI: Dr. Krause.
2 DR. KRAUSE: You know, the trouble with
3 studying HPV is the lack of good tissue culture models
4 in figuring that kind of stuff out, but there are
5 about 50 copies of the HPV genome in a HeLa cell.
6 And, to the extent that has been looked,
7 it appears as though all the components are there.
8 Whether they're completely normal HPV Type 16 or
9 there's something wrong with them, I'm not sure has
10 been looked at.
11 But they appear normal based on the
12 limited studies that have been done.
13 CHAIRPERSON FERRIERI: Dr. Johnston,
14 thanks for your patience.
15 DR. JOHNSTON: Yes, if I may, I'd like to
16 have a question answered and then provide a comment.
17 And this is a question to Andy Lewis.
18 Andy, you presented earlier a very well
19 thought out plan for developing a policy here at CBER,
20 and I'm wondering if there's been given any thought to
21 the time line that it will take to accomplish that
22 plan?
23 DR. LEWIS: There's been some
24 consideration of that. I think that the understanding
25 that I have right now is that there may be resources

1 available to begin with an international workshop on
2 cell substrates sometime between now and next October,
3 probably late in the summer or September.
4 In terms of developing a working document
5 within the organization, I think we have outlined for
6 you what the major components of that document might
7 be. It's not in hand at this point in time, and
8 there's really no serious discussion as to a time
9 frame as when that could be available.
10 But, realistically, I think we could
11 probably have something within six months or so, if
12 that were the way we would go. Beyond that, I don't
13 think we have any perception as to a time line.
14 DR. JOHNSTON: Okay, thank you.
15 My view is that neoplastic cell lines
16 definitely need to be considered aggressively,
17 particularly for situations where there are no
18 alternatives. And I think that the methods, the plan,
19 the approach that has been outlined today is highly
20 reasonable.
21 The resource issues are probably not
22 insignificant; however, I think in general, when one
23 is talking about prevention, we tend to undervalue
24 those technologies, and perhaps this is one area where
25 that undervaluing needs to change and that resources

1 need to be made available to accomplish these tests in
2 an expeditious manner.
3 Now, whether or not one can rely on NIH,
4 I think, is questionable. There is a new vaccine
5 study section, but the degree to which it will look
6 favorably upon very applied applications is yet to be
7 determined because there's just no track record there.
8 So I would caution FDA to first look
9 within before looking without.
10 Now, my concern is actually in contrast to
11 that raised earlier by Dr. Wolfe, and it gets back to
12 a comment made by Dr. Daum earlier, and that is one of
13 risk-benefit ratio. Risk will never be nothing. We
14 all know that.
15 And my concern is not so much that FDA
16 will be precipitous, but that it may be too slow. And
17 I guess one thing I'm uncertain about is where in the
18 equation the risk-benefit discussion will take place.
19 Will this be at a product by product
20 level? And what will happen in cases -- and I'll use
21 the case of HIV vaccine since it was raised -- where
22 the risk-benefit ratio itself will probably be
23 dominated by issues other than cell substrate?
24 And that is the safety of the product
25 itself, as well as the huge potential benefit that it

1 may have.

2 So that is one example where there may not
3 be alternatives to other cell substrates, where there
4 could be substantial risk issues involved in the
5 product itself, where there could be an enormous
6 benefit.

7 And I guess my concern is I would hate to
8 see things not progress because cell substrate issues
9 have not yet been addressed and a policy has not yet
10 been -- you know, something that would be widely
11 applicable to everything has been formalized.

12 CHAIRPERSON FERRIERI: Well, that's very
13 well articulated. Before we take a question from Dr.
14 Nathanson, I wonder if Dr. Hardegree or a member from
15 the Agency would like to respond to Dr. Johnston's
16 point?

17 DR. HARDEGREE: Well, I think that you've
18 heard before that we probably have to consider
19 benefit-risk on a product by product category. And so
20 that, as people are bringing us specific problems and
21 issues, each of those are being considered.

22 And I think you also heard Andy say this
23 morning that, as we have a specific product that we
24 need to bring to this Committee, that we can do that
25 in a way that we may need to address.

1 But it's time to get the discussion going
2 about what the issues are, and so that everybody can
3 be thinking about these together as opposed to a
4 commercial sponsor alone thinking about it with FDA.
5 CHAIRPERSON FERRIERI: Thank you, Carolyn.
6 Dr. Nathanson, I was going to call upon
7 you, but you've volunteered.
8 DR. NATHANSON: I just want to emphasize
9 what several people have said, Peggy Johnston and also
10 Sid Wolfe, about -- number one, I would hope -- the
11 world desperately needs an AIDS vaccine.
12 I would certainly hope that you would put
13 some teeth into the response to this, number one, by
14 including some statements about a time line and about
15 resources. And I certainly don't think it should be
16 left to RFPs and grant applications.
17 This is something that is an applied
18 problem, and there should be money that is
19 specifically put there and a very directed program to
20 accomplish this. And I think that could be a very
21 useful recommendation, so I just wanted to emphasize
22 that.
23 CHAIRPERSON FERRIERI: Well, thank you.
24 I think this is just what Dr. Lewis and other members
25 need to hear from us, and the recordings here are

1 taking this all in.

2 Yes, Dr. Edwards.

3 I need to tell you, Kathy, when you called

4 me the other day, my secretary wrote it down as Dr.

5 Edwards Vanderbilt. And I said I don't know any Dr.

6 Edward Vanderbilt, but then I figured it out.

7 Kathy.

8 DR. EDWARDS: Thank you.

9 Well, first of all, I'm very impressed

10 with the FDA presentation. And it's been certainly

11 lucid and has clearly shown the quality of the science

12 that exists at the FDA in spite of tremendous

13 financial constraints.

14 And I think that that really is a tribute

15 to the productivity and the intellect and hard work of

16 people. And certainly that funding does have to be

17 enhanced in this area because clearly this is a

18 mission of CBER and it's very, very important.

19 Every day I labor in the trenches of

20 trying to convince parents that vaccines are safe, and

21 obviously that is becoming more and more difficult to

22 do.

23 So that I think it is really imperative

24 that, from this meeting, there is a public sentiment

25 and there is real concerted effort to get the funds to

1 the FDA to continue this important work to assure that
2 vaccines are safe.
3 And so that I really think it's a very
4 important practical issue that must be done.
5 CHAIRPERSON FERRIERI: Thanks, Kathy.
6 Dr. Snider and then Dr. Wolfe.
7 No? Okay.
8 Dixie.
9 DR. SNIDER: Several comments. I guess,
10 in summarizing my advice to the FDA, I would say that
11 I think that the emphasis that they placed -- where
12 they placed the emphasis today is understandable, but
13 there are things on the front end and on the back end
14 that need to be looked at just as carefully, need to
15 be discussed publicly.
16 And, for example, the whole business about
17 justifying using certain cell lines, I personally am
18 in favor of it, but the point is that there needs to
19 be some discussion around the alternatives, as I said,
20 for traditional substrates as opposed to novel
21 substrates and the whole risk-benefit thing we've been
22 talking about, you know, compared to what
23 alternatives.
24 And it seems to me that really needs to
25 take place early on, especially from a manufacturer's

1 point of view, before there is too much investment in
2 a particular approach. And so I think that needs to
3 be given more consideration.
4 And then, to just echo again what I said
5 earlier and what Tom has said, I think on the back end
6 -- I mean, no matter what we do in terms of monitoring
7 production and monitoring safety during the early
8 phases of development, there are going to -- new
9 issues are going to come up or old issues are going to
10 hang on.
11 And so there is the issue of monitoring
12 folks during the randomized trials and during post
13 marketing surveillance. And it raises all the issues
14 again of what mechanisms are you going to use to
15 monitor people who have been recipients of these
16 vaccines.
17 And I think the public's going to want
18 that kind of an assurance. And it's not too early to
19 begin to think about some paradigm for that, as well
20 as a paradigm for, you know, checking out whether
21 certain proteins or viruses or cells or DNA slips
22 through in a manufacturing process.
23 CHAIRPERSON FERRIERI: Thanks, Dixie.
24 DR. SNIDER: And finally, the
25 tumorigenicity thing I want to bring up again because

1 -- on the record, that it's not just NIAID, it's NCI.
2 But somehow, I think it's important to understand
3 mechanisms and mobilize the research community around
4 conducting some studies to find out mechanisms.
5 I think it's going to be a challenge. And
6 maybe NVPO can help, maybe others can help, but it's
7 important to engage on this issue.
8 CHAIRPERSON FERRIERI: Thanks. That
9 overlaps very much into the second question, and I'm
10 grateful for your doing that. A couple other points.
11 First Dr. Huang, and then Caroline Hall, and then Dr.
12 Daum.
13 DR. HUANG: When I look at CBER's approach
14 to evaluating neoplastic cell lines, I basically see
15 two major worries. One is tumorigenicity and the
16 other one is adventitious agents.
17 I'm quite comfortable with the first
18 approach and the worry about tumorigenicity. I think
19 that, in fact, some of the tests may be overkill.
20 This is in particular when we begin to think about
21 more recent knowledge of how cancer cells are actually
22 formed.
23 It's a progression, multi-step
24 progression.
25 And I believe that one of the papers that

1 we got earlier to read really did mention this. And
2 so, on that particular line, if we see oncogenes or
3 sequences of oncogenes or partial oncogenes around,
4 I'm not terribly worried about that aspect.
5 However, with adventitious agents, I would
6 just like to add my bit to the worry about those
7 agents that might cause slow viral disease or
8 neurological disease that we don't know a whole lot
9 about.
10 And more specifically, I think that, of
11 the cell lines that were used to test for adventitious
12 agents, I would suggest that one of the cell lines
13 that be used and which is used regularly in diagnostic
14 laboratories is the 293 cell line which will pick up
15 many humantrophic agents that other cells may not.
16 So that's a very specific sort of
17 suggestion.
18 CHAIRPERSON FERRIERI: Thank you, Alice.
19 Dr. Hall.
20 DR. HALL: I just want wondered if Dr.
21 Lewis could explain or clarify a little more about the
22 document that will be available in about six months.
23 You said the time line. What this will
24 contain or how it will be utilized. Is this something
25 that would be given to a potential manufacturer and

1 then the burden is upon them to get these tests, to do
2 these tests? And it brings up the questions of
3 standardization, etc.
4 DR. LEWIS: The perception that I would
5 have of the document -- it might be ready in six
6 months -- would be something that we'd be discussing
7 internally and that we would be having other people
8 look at in any type of forum that's necessary.
9 And if we had and we organized a meeting,
10 say, sometime in August or September, if that document
11 were ready, certainly it could be a part of a session
12 or part of a day or whatever for discussion at that
13 meeting.
14 I think to -- my perception would be that
15 it would be premature to have this as a guidance
16 document at this point in time at this stage of its
17 development to be submitted to industry. That would
18 only be ready after these discussions, and perhaps
19 even after more discussions.
20 Because once we get into this process, it
21 may be somewhat open ended. And how long it might
22 take to come up with a guidance document I think might
23 be unpredictable. Certainly I don't think we would
24 stop having to deal with these problems as they come
25 up, and we'd just have to manage as best we can.

1 But again, if the question is to when
2 there may be a guidance document ready, I think it
3 would not be ready in six months. That would be my
4 perception. Dr. Eagan or Dr. Hardegree may have other
5 things to say about that.
6 CHAIRPERSON FERRIERI: Thank you, Andy.
7 Dr. Daum. And appreciate, Bob, if you
8 might segue into the second question.
9 DR. DAUM: Yeah, I think somewhere between
10 the first and the second, but certainly there will be
11 some second question comments.
12 In sitting here sort of thinking about all
13 of this, it seems to me that there's sort of three
14 orbs or circles that are -- need to spin all at once
15 to try and get arms around these issues. And one is
16 the -- what is the need to pursue this new technology?
17 And we haven't heard as much about that as
18 I would like partly for -- mainly proprietary reasons.
19 But we heard some of them in theoretical context.
20 But I think the need is a crucial thing
21 because I think there's an education process here
22 that's got to go on to sell the scientific community
23 and the public beyond about the need for new
24 technologies.
25 Comes with the need for new technologies

1 is careful monitoring strategies, sort of sphere
2 number two. And I've been very impressed this morning
3 at the sincerity, at the thoroughness and at the
4 scientific integrity of plans to monitor these new
5 technologies as they go forward with everything that's
6 known about what to monitor.
7 But I think that there's also another
8 sphere sort of orbiting around here which we're all
9 trying to come to grips with somehow, is that comes
10 with any new technology risks that we don't know much
11 about at this point.
12 And I think that for people to accept
13 these risks and believe that they're important to take
14 is going to again come around to the education process
15 about what is the need and what is driving pursuit of
16 these new ideas.
17 And so I would like to add something that
18 I haven't heard much so far, is that there needs to be
19 some kind of education process of the scientific
20 community and perhaps of the public beyond about the
21 need for new technologies and new ideas and what's
22 being done to monitor them carefully.
23 So, to me these three things are sort of
24 spinning around at once. And the vast majority of
25 what we've heard and are able to comment on is what is

1 CBER's approach to new technologies with existing
2 ideas and looking for existing transmissions, for
3 instance, of infectious agents.
4 And there's a couple of areas that
5 they're, by virtue of the beast, unable to comment on.
6 And I think education and acceptance by us, that the
7 risks may be worth it and let's go forward together
8 with our eyes wide open has to be the approach.
9 CHAIRPERSON FERRIERI: Thanks, Bob.
10 Dr. Oxman and then Dr. Eickhoff.
11 DR. OXMAN: Just to expand a little bit on
12 a point that Dixie Snider mentioned a couple of
13 minutes ago, most of what we've seen so far is an
14 approach to dealing with a vaccine produced in a
15 potentially neoplastic substrate and then trying to
16 minimize the risk.
17 One of the best ways of minimizing the
18 risk is to start off by choosing the better of two or
19 three or ten substrates and how to do that. And I
20 think more effort needs to be put into that.
21 I realize it's difficult, because of the
22 position of the FDA, to dictate what substrates people
23 should use. I've been around long enough to see that
24 many substrates are chosen quite at random and
25 serendipitously.

1 And once an investment is made, often by
2 accident, people are reluctant to change the
3 substrates. There are -- neoplastic cell substrates
4 cover a very broad territory.
5 And the risks involved in manipulating an
6 already well characterized transformed cell, for
7 instance, by inserting a gene that would express CD4
8 on its surface to make it suitable as a substrate for
9 HIV, this would be a much lower risk and an easier
10 thing to deal with in terms of guaranteeing safety
11 than an uncharacterized or a much less characterized
12 neoplastic cell line.
13 So I think emphasis on the choice of
14 substrates prospectively would be very useful.
15 CHAIRPERSON FERRIERI: Thank you.
16 Dr. Eickhoff.
17 DR. EICKHOFF: Thanks.
18 I'd like to thank the presenters this
19 morning, as others have already done, for really a
20 very elegant series of discussions of the current
21 state of using neoplastic cell lines for vaccine
22 production.
23 I think it is a -- as others have said
24 also, it's a very reasonable approach. And I think
25 also it's a very necessary approach because one gets

1 the impression, at least I did, that this whole
2 approach is really a bit of a freight train that is
3 pounding down on CBER and we better start learning how
4 to deal with it now rather than waiting for some
5 product license application that uses this technology
6 and then suddenly there will be a real problem on our
7 hands.

8 The process that is proposed -- as I said,
9 it's a very reasonable one. I think it should --
10 obviously the science is going to be the determinative
11 discussion. But it should also be a very public
12 process, I think, and I would really like to emphasize
13 that.

14 Not only because public advocacy is
15 probably going to be necessary to provide the
16 necessary resources, which are uncertain at best, but
17 also because -- and here I'd like to take off on what
18 Dr. Daum said because I think this is terribly
19 important.

20 There's going to have to be an enormous
21 amount of public education. The public today is a
22 very different public than it was 30 years ago when
23 polio vaccine came on the market and the response was,
24 "Does it work? Here, give it to me."

25 There were no concerns about safety for

1 obvious reasons, and today there are. The public, for
2 a whole variety of reasons which we don't need to go
3 into now, has become much more distrustful of the
4 vaccine enterprise, if you will.
5 At least many segments of the public are.
6 And when they hear about vaccines produced in
7 neoplastic cells, that will set some people's teeth on
8 edge. And so I think the public education process is
9 going to have to be enormously important.
10 CHAIRPERSON FERRIERI: Thank you, Ted.
11 I was volunteered as a youngster for the
12 early Salk trials, so I feel I'm very sensitive to
13 these issues. I undoubtedly have a little SV40 around
14 and I don't worry about it at night, but I do care a
15 lot about what we're doing now and in the future
16 certainly.
17 Other comments?
18 Yes, please.
19 DR. SCHILD: I feel very privileged to
20 have been able to come to today's debate. I think the
21 FDA has done a superb job in presenting, with great
22 clarity, the complexities and urgency of these issues.
23 And I think their proposals are warmly received.
24 One thing is key, and that is the need for
25 more regulatory research. And I think it's absolutely

1 right that Government funded bodies have the major
2 role in this field of research. Industry would like
3 to do more, but I think getting the new products out
4 is a major priority.
5 These issues are of global significance.
6 And there is -- I'm sure there is good spirit of
7 global cooperation. I think the various regulator
8 authorities in the world will work together on issues
9 and share out the challenge.
10 One other thing I'd like to mention is
11 that all biological products of the type we've been
12 discussing today are really very much the function --
13 their characteristics are very much a function of the
14 cells in which they were produced.
15 The measles vaccine made in chicken cells
16 doesn't work in the same way exactly as measles
17 vaccine made in human diploid cells. Influenza virus
18 grown in one substrate is different from that grown in
19 another.
20 And when we're considering the first part
21 of this, evaluating in neoplastic cells, we have to
22 take into account also the characteristics of the
23 products produced in those cells and how cells affect
24 those as part of that consideration.
25 Thank you.

1 CHAIRPERSON FERRIERI: Thank you, Dr.
2 Schild. I'm so pleased that you could join us on the
3 panel today.
4 Let's keep up this crescendo here.
5 Dr. Greenberg.
6 DR. GREENBERG: Well, at the risk of being
7 repetitive, I am in agreement with much that is said
8 here. But I think we have to remember that we, here
9 on the Committee, have listened to, in my span on the
10 Committee, about a year and a half of decreasing
11 funding for any form of research, and we're hearing a
12 very important need.
13 And everything I have learned up to this
14 point would say that the resources are not presently
15 available to carry out this need. And so, if there's
16 any single message that I would like to give from this
17 Committee -- to the Government from the Committee, is
18 that those resources have to be available.
19 Otherwise it's sort of silly to be asking
20 us this question.
21 CHAIRPERSON FERRIERI: Well, I agree
22 completely. And I like to think that comments like
23 yours and others will be picked up by the national
24 media. We're frequently bugged so much about the
25 things we discuss here. We can't control what the

1 translation is.

2 So, if you're out there in the audience,

3 I hope you're hearing this, that you're quoting

4 members who have said it. This is the third or fourth

5 time. We are all very worried about the financial

6 structure of CBER, other elements of FDA as well.

7 And this is an example of the vitality,

8 the critical need to back this up. Otherwise we

9 shouldn't be in the business, in my opinion, if we

10 can't pursue this in depth.

11 And a great deal of money is wasted in

12 Government for things that I am politically sensitive

13 to not enumerating for you all today, but I think that

14 the nation's health is the subject here that we're

15 gripping with.

16 Yes, Dr. Adimora.

17 DR. ADIMORA: I wanted to, very briefly,

18 revisit the issue of the risks and benefits in various

19 target populations, and just revisit the issue of what

20 would be the arena in which these issues would be

21 decided.

22 Specifically, I think what I mean is that

23 there are risks and benefits of vaccines that are

24 manufactured in these continuous cell lines, and the

25 extent to which these risks and benefits change -- the

1 extent to which these risks and benefits change
2 certainly varies with the anticipated target
3 population.

4 For example, in HIV, if one thinks about
5 the critical need for an HIV vaccine, there are
6 clearly very different risks and benefits associated
7 when you're thinking about a child growing up, say, in
8 some part of Central Africa who might have, for
9 example, a 50% chance of ultimately dying of HIV at
10 some point in his or her life compared to the same
11 risk of a child growing up in suburban America.

12 On the other hand, risks and benefits can
13 certainly vary among inhabitants of even the same
14 country -- obviously within different subpopulations
15 of the same country.

16 I'm normally very conservative by nature,
17 but one concern that I have is that some of the -- I'm
18 sort of uncertain how to say this, but I'm concerned
19 that intense focus on -- and I'm not saying that this
20 is not -- that this is unwarranted, but I think that
21 I worry about the extent to which intense focus on
22 very small risks in some populations may inhibit the
23 development of vaccines in populations in which such
24 vaccines could do immediate good to huge numbers of --
25 to people who are at incredibly high risk.

1 And I'm not sure how to approach this
2 issue or even who should approach it, but I just
3 thought that it was a reasonable issue to throw out
4 concerning your questions for number two.
5 CHAIRPERSON FERRIERI: I think that if
6 Mary Lou had been with us, she would have been able to
7 relate to that point and be a champion of what you
8 have just said.
9 Other points?
10 Dr. Lewis, have you heard enough today
11 that will help you all? We'll start the collection
12 tin in a moment.
13 (Laughter.)
14 But I would like to be able to sum up very
15 briefly. I want to congratulate the panel, the
16 permanent members of the Committee, and the wonderful
17 guests we had today to make this very dynamic beyond
18 my hopes and expectations, I might say.
19 And so I hope that FDA has benefitted from
20 it. I think the critical things that we have heard
21 today that relate to the current approach of
22 evaluation include the reasonableness of the approach,
23 how critical it is to take these approaches; and that,
24 although some things may appear to be in excess, most
25 of the approaches can be defended.

1 The need for the financial resources is
2 evidence. We don't have confirmation or affirmation
3 that those resources will be available, and we need to
4 recruit public advocacy in the strongest way and their
5 interest in education of the public to be on the same
6 band wagon so that we're all together as this moves
7 forward.
8 We all have an investment in this.
9 The other items that were brought up
10 include a need to better understand the mechanisms of
11 what we are dealing with and what is being studied,
12 not just a simple pragmatic approach, and if the
13 resources could accommodate pursuing that.
14 And we can't be at all dependent that
15 other elements of the Federal Government such as NIH
16 will be able to pursue that, so we're going to have to
17 be very creative in thinking of how we're going to
18 understand this and support basic understanding of
19 these lines.
20 Alternatives have been suggested as well.
21 Although the focus has been neoplastic cell lines,
22 that we consider other novel, creative substrates as
23 we move forward. Monitoring strategies of these new
24 technologies have also been emphasized, and trying to
25 move forward in a very prospective way in examining

1 alternative choices.

2 And the choice of substrate need not be

3 confined to the historical past. And although those

4 who come to FDA already have chosen their cell

5 substrate, it doesn't mean that the word can't get out

6 from now on that don't be confined and fettered by the

7 past.

8 We look forward and throw back to FDA the

9 need to see a document that you would prepare

10 internally, and would encourage its review at a

11 special session, for example, of the workshop that is

12 being proposed by early fall.

13 I think that sums everything up, but I

14 think that the inclusion of the public in this process

15 is very vital. And I encourage whatever mechanisms we

16 might have of public relations, other ways of

17 disseminating information that can be understood by

18 everyone for people who do not do molecular biology by

19 day and night.

20 So, I'd like us to break for lunch. And

21 those of us who are included in the closed session at

22 1:30, we will start promptly.

23 Thank you all very much.

24 (Whereupon, the proceedings were adjourned

25 at 12:26 p.m.)

**CERTIFICATE**

This is to certify that the foregoing transcript in the

matter of: VACCINES AND RELATED BIOLOGICAL PRODUCTS ADVISORY COMMITTEE MEETING

Before: DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE

Date: NOVEMBER 19, 1998

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