# Transcript of

**Case:** TSE Advisory Committee Meeting

**Date:** July 17, 2003

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UNITED STATES OF AMERICA

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FOOD AND DRUG ADMINISTRATION

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TRANSMISSIBLE SPONGIFORM ENCEPHALOPATHIES

ADVISORY COMMITTEE (TSEAC)

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BETHESDA, MARYLAND

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WEDNESDAY,
JULY 17, 2003

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The Advisory Committee met in the

Versailles Room at the Holiday Inn Select, 8120 Wisconsin Avenue, Bethesda, Maryland 20814, at 8:00 a.m., with Suzette A. Priola, Ph.D., Chair, presiding.

PRESENT:

SUZETTE A. PRIOLA, Ph.D., Chair

JOHN C. BAILAR, III, M.D., Ph.D., Member
ARTHUR W. BRACEY, M.D., Member
LISA A. FERGUSON, D.V.M., Member
PIERLUIGI GAMBETTI, M.D., Member
R. NICK HOGAN, M.D., Ph.D., Member
RICHARD T. JOHNSON, M.D., Member
RIMA F. KHABBAZ, M.D., Member

SIDNEY M. WOLFE, M.D., Member
CHARLES E. EDMISTON, JR., Ph.D., Temporary Voting Member, Topics , 3 & 4
KENRAD E. NELSON, M.D., Temporary Voting Member, Topics 2, 3 & 4
TERRY V. RICE, Temporary Voting Member, Topics 2, 3 & 4

DAVID F. STRONCEK, M.D., Temporary Voting Member, Topics 2, 3 & 4
SHIRLEY J. WALKER, Consumer Representative
STEPHEN R. PETTEWAY, JR., Ph.D., Non-Voting Industry Representative
SHEILA D. LANGFORD, Staff

ALSO PRESENT:

DR. DAVID M. ASHER, OBRR, CBER, FDA
DR. STANLEY BROWN, CDRH
DR. YUAN-YUAN CHIU, CDER, FDA
DR. MICHAEL DUNN, V. Pres., Chairman of the Regulatory
Committee, GMIA
DR. JAY EPSTEIN, Director, OBRR, CBER, FDA
DR. ROBERT HILLS, Health Canada, Ottawa

DR. GEORGE MASSON, President GMIA
DR. TERRY MORRIS, APHIS
DR. PEDRO PICCARDO, CJD
DR. MORRIE POTTER, CFSAN, FDA
CAPTAIN EDWARD RAU, Environmental Health Officer, NIH
DR. RON ROGERS, Health Canada, Ottawa
DR. ROBERT ROHWER, Director Molecular Neuro-Virology

Unit, VA Medical Center, Baltimore
DR. WILLIAM RUTALA, UNC
REINHARD SCHRIEBER, Chief Manufacturing Officer,
Deutsche Gelatine
DR. ROBERT SOMERVILLE, IAH Edinburgh, UK
FABRIKEN STOESS, AG, Gelita Group
DR. DAVID TAYLOR, SEDECON 2000, UK

NELSON BROOKLANG, Ortech International
DANIEL R. DWYER, ESQ., Kleinfeld, Kaplan & Becker,
Counsel to GME
CHARLES FILLBURN, Nutranax Laboratories
PAUL HAFFENDEN, TerraCell
MERLYN SAYERS, M.B., B.Ch., Ph.D., Carter BloodCare
WAYNE E. VAZ, Serologicals Corporation

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

2 8:03 a.m.

3 SECRETARY FREAS: Dr. Priola, members of

4 the public, invited guests and public participants, I

5 would like to welcome all of you to this our 14th

6 meeting of the Transmissible Spongiform

7 Encephalopathies Advisory Committee. I am Bill Freas.

8 I am the executive secretary for this Committee. At

9 this time, I would like to go around and introduce to

10 you the members at the head table, starting on the

11 right hand side of the room.

12 The first chair will soon be occupied very

13 shortly by Dr. Pierluigi Gambetti. He is a professor

14 and director Division of Neuropathology Case, Western

15 Reserve University. Okay. Then the second chair will

16 soon be occupied by Dr. Richard Johnson, professor of

17 neurology at Johns Hopkins University. And then going

18 around the table, the people who are here, Dr. Arthur

19 Bracey, associate chief Department of Pathology, Saint

20 Lukes Episcopal Hospital. Next is Dr. Lisa Ferguson,

21 a senior staff veterinarian, U.S. Department of

22 Agriculture.

23 Next is Dr. Nick Hogan, associate

24 professor of ophthalmology, University of Texas,

25 Southwestern Medical School. Next is Dr. Rima

1 Khabbaz, associate director for Epidemiologic Science,
2 National Center for Infectious Diseases, Atlanta,
3 Georgia. Around the corner of the table is a
4 gentleman, whom I'm going to ask to join us at lunch
5 time, if that is okay, Dr. Nelson. Could I ask you to
6 join us at lunch time instead of in the morning?
7 DR. NELSON: Certainly.
8 SECRETARY FREAS: This is my mistake. I
9 apologize. Dr. Nelson will be a temporary voting
10 member, and he will join us right at lunch time, and
11 if you could just sit over in the FDA section up until
12 Topic 1 is over. And when I read the Conflict of
13 Interest statement, hopefully, that will be explained.
14 My apologies for not checking before I started. Okay.
15 Next is our Chair, Dr. Suzette Priola.
16 She is an investigator of Laboratory of Persistent and
17 Viral Diseases of the Rocky Mountain Laboratories.
18 Next is our consumer representative, Ms. Shirley
19 Walker, vice president of the Health and Human
20 Services, Urban League of Greater Dallas in north
21 central Texas. Next is Dr. Sidney Wolfe, director of
22 Public Citizen Health Research Group, Washington, D.C.
23 Next is Dr. John Bailar, professor in
24 America's University of Chicago. Next is our non-
25 voting industry representative, Dr. Stephen Petteway,

1 director of Pathogen Safety and Research, Bayer
2 Corporation. Three Committee members in addition to
3 the two that are joining us shortly could not be with
4 us at all for this meeting. They are Mr. Val Bias,
5 consumer representative, Lynn Creekmore, staff
6 veterinarian and Dr. Stephen DeArmond from the
7 University of California.
8 I would now like to read into the public
9 record the Conflict of Interest statement for this
10 meeting. "The following announcement is made part of
11 the public record to preclude even the appearance of
12 a Conflict of Interest at this meeting. Pursuant to
13 the authority granted under the Committee Charter, the
14 Director Center for Biologics Evaluation and Research
15 has appointed Mr. Terry Rice and Drs. Kenrad Nelson,
16 who I just asked to leave the table, and David
17 Stroncek as temporary voting members for Topics 2, 3
18 and 4 of this meeting.
19 In addition, the associate commissioner of
20 External Relations of FDA has appointed Dr. Charles
21 Edmiston as a temporary voting member for Topics 2, 3
22 and 4 of this meeting. Based on the agenda, it has
23 been determined that the Committee will not be
24 providing advice on specific firms or products at this
25 meeting. The topics deemed discussed by the Committee

1 in open session are considered general matters issues.
2 To determine if Conflicts of Interest
3 exist, the Agency reviewed the agenda and all relevant
4 reported financial interests from meeting
5 participants. The Food and Drug Administration
6 prepared general matters waivers for special
7 Government employees, who required a waiver under 18
8 U.S. Code 208. Because general matters topics impact
9 on so many entities, it is not prudent to recite all
10 potential Conflicts of Interest as they apply to each
11 member.
12 FDA acknowledges that there may be
13 potential Conflicts of Interest, but because of the
14 general nature of the discussion before the Committee,
15 these potential conflicts are mitigated. We would
16 like to note for the record that Dr. Stephen Petteway
17 is serving as a non-voting industry representative
18 member for this Committee. He is employed by Bayer
19 and thus has interests in his employer and other
20 similar firms.
21 Listed on the agenda are speakers making
22 industry presentations and/or updates. These speakers
23 have financial interests associated with their
24 employer and with other regulated firms. These
25 speakers were not screened for these Conflicts of

1 Interests. With regard to FDA's invited guest
2 speakers, that's all other speakers, except those from
3 industry, the Agency has determined that the services
4 of these speakers are essential.
5 The following interests are being made
6 public to allow the meeting participants to
7 objectively evaluate their presentations and comments
8 that they may make. Dr. Robert Rohwer has disclosed
9 he has financial interest with various firms that
10 could be affected by the Committee discussions. Dr.
11 William Rutala receives consultant fees from several
12 firms that could be affected by the Committee
13 discussions. Dr. Robert Somerville has research
14 supported by the Gelatin Manufacturers of Europe. His
15 expenses to this meeting were also paid by the Gelatin
16 Manufacturers of Europe. Dr. Charles Weissmann holds
17 patents related to Prion Disease work.
18 Members and consultants are aware of the
19 need to exclude themselves from the discussions
20 involving specific products or firms which they have
21 not been screened for the Conflict of Interest. Their
22 exclusion will be noted in the public record. With
23 respect to all other meeting participants, we ask, in
24 the interest of fairness, that they address any
25 current or previous financial involvement with any

1 firm whose product they may wish to comment upon.
2 Waivers may be available by written request to the
3 Freedom of Information Office."
4 That's the end of the Conflict of Interest
5 statement. I do ask that throughout this meeting
6 before it starts if you would check your cell phone or
7 your pager and, please, put it in the silent mode, so
8 it won't disrupt those people sitting next to you.
9 Next, the FDA is continually trying to
10 improve its Advisory Committee Program and to reduce
11 any perceived Conflicts of Interest. It has asked Dr.
12 Katherine McComas from the University of Maryland to
13 conduct a survey of this program, and I would like to
14 give her the opportunity to tell us how we can help
15 her with this survey and how the survey is being
16 conducted. Dr. McComas, either place. Keep talking
17 and they'll turn the mike volume up.
18 DR. MCCOMAS: Okay. Good morning and
19 thank you. I'm Katherine McComas and I'm a faculty
20 member at the University of Maryland, and I'm here
21 today to conduct a study of what people know and
22 understand about the Conflict of Interest procedures
23 that the FDA uses to monitor real or potential
24 Conflicts of Interest of its Advisory Committee
25 members. This is a study that is being conducted

1 across multiple meetings. This is the 11th meeting I
2 have attended across the centers at FDA, including
3 CBER.
4 For those of you in the audience, I've
5 distributed a questionnaire on your chair and I have
6 also distributed a different questionnaire to the
7 Advisory Committee members. If you have an
8 opportunity today to complete this questionnaire or
9 tomorrow, there is a box on the registration desk
10 where you can drop it. Otherwise, there is a business
11 reply envelope that you can just drop it in the mail
12 as soon as you can. Your participation is voluntary,
13 but it is important. The more responses we get, the
14 better we are to provide feedback to the FDA about
15 what people know and understand about the Conflict of
16 Interest procedures, and what may be done to improve
17 satisfaction, if necessary, with the Advisory
18 Committee process.
19 Again, I appreciate your participation and
20 if you have any questions, my contact information is
21 included in the letter, in the questionnaire and I
22 would be happy to provide any answers. Also, when the
23 study is done, the responses will be available in
24 summary form to everyone who is interested. So thank
25 you very much for your time and have a great day.

1 SECRETARY FREAS: So if you got here early
2 and did not receive a questionnaire, the
3 questionnaires are on the table outside and, please,
4 everybody on the FDA staff will be more than glad to
5 help you if you have any questions with this
6 questionnaire.
7 Dr. Priola, I turn the microphone over to
8 you to start the meeting. Thank you.
9 DR. PRIOLA: So since we have a very full
10 agenda today, we will just get started with the first
11 speaker, who is Dr. Potter, who will give us
12 background on Topic 1.
13 DR. POTTER: Good morning. FDA has been
14 considering the safety of gelatin with regard to BSE
15 for a number of years, and has come to this Committee
16 on a number of occasions to get its recommendations on
17 FDA's guidance to gelatin manufacturers and users.
18 The safety of gelatin is determined as you've told us
19 before by the safety, the source materials in the
20 degree to which the gelatin manufacturing process
21 destroys prions that enter the system.
22 Questions to the Committee have dealt with
23 these two factors and how well knowledge about TSE's
24 was reflected in FDA guidance for assuring the safety
25 of gelatin for food and cosmetic use. Before 1996,

1 FDA did not include gelatin within its recommended
2 restrictions concerning bovine ingredients in FDA
3 regulated products. In 1996, FDA began to review its
4 position on gelatin in light of new information that
5 associated BSE exposure with Variant CJD in humans and
6 new data from a study on the effect on infectivity of
7 gelatin processing that suggested only partial
8 effectiveness.
9 In 1997, this Committee met to consider
10 the safety of gelatin and to provide an assessment on
11 the overall risk to humans associated with imported
12 gelatin. This Committee made the following
13 observations: First, that the scientific information
14 available no longer justified excepting gelatin from
15 restrictions recommended by FDA for other bovine
16 derived materials from BSE countries. Second, that
17 bovine gelatin injected or implanted forms posed a
18 higher risk of transmitting BSE to humans than gelatin
19 that is ingested. Third, that brains and spinal cords
20 from cattle from BSE countries should be excluded from
21 raw materials used to produce gelatin for human
22 consumption. Fourth, alkaline or acid processing in
23 gelatin manufacturer may only reduce rather than
24 eliminate BSE infectivity, and the Committee called
25 for better validation studies, particularly to

1 investigate the other steps of gelatin manufacture.
2 And finally, that porcine gelatins appear to pose no
3 known risk of transmitting TSEs to humans.
4 After the 1997 TSEAC meeting, FDA issued
5 its gelatin guidance document which remains the
6 current FDA position in policy on the production of
7 gelatin. In this guidance, FDA proposed the following
8 recommendations concerning the acceptability of
9 gelatin in FDA regulated products intended for human
10 use. First, that importers, manufacturers and
11 suppliers should determine the tissue, species and
12 country source of all materials used in processing
13 gelatin for human use.
14 Second, that bone and hides from cattle
15 from any source country that show signs of neurologic
16 disease should not be used as raw materials. Third,
17 gelatin production from bones and hides obtained from
18 cattle that reside in BSE countries or countries that
19 do not meet the latest BSE related OIE standards
20 should not be used in injectable, ophthalmic or
21 implanted FDA regulated products or in their
22 manufacture, but may be used in FDA regulated products
23 for oral consumption and cosmetic use by humans if the
24 cattle come from BSE-free herds and if the slaughter
25 house removes heads, spines and spinal cords directly

1 after slaughter.

2 Fourth, gelatin produced from bovine hides
3 from any source country may be used in FDA regulated
4 products for oral consumption and cosmetic use by
5 humans if processors insure that the hides have not
6 been contaminated with brain, spinal cord or ocular
7 tissues of cattle residing in or originating from BSE
8 countries. Fifth, gelatin produced from bovine hides
9 and bones may be used in FDA regulated products for
10 human use if the gelatin is produced from raw
11 materials from countries like the United States that
12 observe OIE standards and have not diagnosed BSE in
13 their national cattle herd, that is RBSE-free. And
14 finally, gelatin produced from porcine skins from any
15 source country may be used in FDA regulated products
16 for human use.

17 In 1998, this Committee met again to
18 discuss gelatin among other issues. FDA's guidance,
19 based on the 1997 TSEAC recommendations, was presented
20 to the Committee to consider several new pieces of
21 relevant information. For example, the infectivity of
22 dorsal root ganglia and low level infectivity in bone
23 marrow and the growing number of BSE cases being
24 discovered in Europe. The Committee considered this
25 new information and decided gelatin could be safely

1 sourced from bones and hides of cattle in BSE
2 countries as long as the recommendations in the
3 guidance were met. That is that the cattle came from
4 BSE-free herds and the high-risk materials were
5 removed after slaughter.
6 And this is at present the status of the
7 safe source factor for gelatin. Continuing on with
8 the other key factor, that of validated effectiveness
9 in the manufacturing process, in June 2001, the
10 Committee was given an update from the Gelatin
11 Manufacturers of Europe on the interim validation
12 study results on the inactivation of BSE through the
13 gelatin manufacturing process. This was an
14 information sharing meeting only and no questions were
15 posed to the Committee.
16 The Committee reviewed the study design
17 and the preliminary data and requested a presentation
18 of the final results as soon as they were available.
19 The Committee is now about to get its wish as GME will
20 present their completed studies, and we will hear
21 other marketing and manufacturing information on
22 gelatin in North America and Europe. After you have
23 heard this new information, we would like you to
24 comment on the studies and to consider the current
25 gelatin guidance in light of these completed studies

1 and other relevant information.
2 And I think, according to my schedule,
3 Yuan-Yuan will now charge up the Committee. Thank
4 you.
5 CHAIR PRIOLA: Thank you, Dr. Potter. Dr.
6 Chiu will now present the questions for Committee.
7 DR. CHIU: Good morning. First, I would
8 like to thank Dr. Priola and the Committee members to
9 take the time to come out and also we have sent you a
10 huge package, gelatin studies protocols and procedures
11 and the results. We appreciate how much time you need
12 to really review those studies. In the early days, in
13 the 1998 year, when the Agency and the Committee
14 together made a decision for the Agency's
15 recommendation on gelatin was based on previous study
16 which the Committee thought was somewhat flawed.
17 So generally, this reason follows the
18 advice of the Committee to then redesign the studies
19 and then today, you know, we have the new study
20 results. You did not review the interim results, but
21 today we have the final results off of five studies.
22 We're hoping, you know, with the presentation today
23 and the background information you have you will be
24 able to help the Agency to answer two questions.
25 Next slide, the first question is "Do

1 those results of these new studies demonstrate a
2 reduction in infectivity that is sufficient to protect
3 human health?" And we are only limited to hear the
4 question to bovine bone gelatin is consumed by humans
5 through oral or topical administration. The question
6 is not for gelatin of other administrations, such as
7 the injection, you know, implantable. We would like
8 the Committee to focus on oral and topical
9 administration.
10 Next slide, now, the first question, you
11 know, the answer could be yes or no or in between
12 regardless, you know, the answer we also would like
13 you to answer the second question. There are two
14 parts. The first part is "Do the scientific data and
15 the information available support the current FDA
16 recommendations on bovine bone gelatin for oral and
17 topical administration?"
18 The current recommendations, next slide,
19 is on this slide. The general policy of FDA is for
20 FDA regulated products, the bovine derived material
21 should come from cattle not bone residing as
22 slaughtered in BSE countries, but the Agency also
23 provides some exemptions. The exemption could be a
24 total exemption unconditional, such as milk, dairy
25 products and the milk derived product. But some of

1 the substances, you know, the Agency provide
2 conditional exemptions, and the gelatin for oral and
3 topical use are giving conditional exemptions.
4 So if the cattle actually is coming from
5 BSE countries, then that condition is the cattle must
6 be from a BSE-free herd and also at the slaughter
7 house the head, the spine and spinal cord should be
8 removed. And this is from BSE countries. Now, some
9 countries may not have BSE cases, but there is
10 consider of high-risk of BSE. Then the recommendation
11 is the heads, the spine and the spinal cord should be
12 removed as the first step in the slaughter house. So
13 the first question is whether this current
14 recommendation still is valid, based on the scientific
15 information we have today.
16 Next slide, if the answer is yes, then
17 that's the end of it. If the answer is no, then we
18 would like to know what changes the Committee would
19 like to recommend to our current policy. The changes
20 can be in all different directions. You may consider
21 we can actually grant a total exemption to the gelatin
22 for oral and topical use or you may consider to modify
23 the current recommendation the FDA has, either by
24 strengthening or by relaxing the conditions. So we
25 are anxious and grateful you will give Agency your

1 deliberation. Thank you.
2 CHAIR PRIOLA: Okay. Thank you, Dr. Chiu.
3 Our next speaker is Mr. Masson, who will discuss
4 market trends in the U.S.
5 DR. MASSON: Yes, good morning everybody.
6 Madam Chairman, I would just like to thank the
7 Committee and the FDA, in particular, about the
8 opportunity to address the Committee. As we have
9 heard from Drs. Potter and Chiu, it has been a long
10 and winding road, the saga of gelatin, and we hope
11 today that we can reach a satisfactory conclusion and
12 see gelatin taken off the file, so to speak, having
13 reassured you of its safety.
14 My first slide, please. Can I have the
15 first slide, please? Okay. Thank you. Well, just an
16 introduction of I'm currently the president of our
17 industry association, the GMIA, and also president and
18 CEO of one of its members at Russelot. The next
19 slide? A bit of history as to GMIA and credentials,
20 so to speak. Our association was formed in 1956. We
21 have six members, all NAFTA based, four from the U.S.,
22 one in Mexico and one in Canada. And we've listed
23 here the typical working committees by which we run
24 the institute. There is no particular order of
25 precedence, but the technical and regulation

1 committees as you can imagine, indeed, are the primary
2 focus of most of our work, I guess.
3 Next, in terms of what we represent, we,
4 as you see, represent roughly 22 percent of the global
5 gelatin production, and almost 100 percent of all the
6 gelatin made in North America. And, indeed, three of
7 our members are also affiliates of the Gelatin
8 Manufacturers of Europe. And I should have added
9 actually that one of the other members is an affiliate
10 of the Japanese Gelatin Manufacturing Group.
11 Next, please. This lists our objectives.
12 As you see, we try to monitor and inform our members
13 of any and all regulations which can impact gelatin.
14 We are the liaison with FDA, USDA and other regulatory
15 authorities, and we gather and distribute technical
16 information to our members, endeavor to promote a
17 broader knowledge of gelatin and encourage its wider
18 consumption. And we provided the forum as you've seen
19 from our committee information on all of the major
20 aspects concerning technical, environmental and safety
21 issues.
22 And as time has gone by and as other
23 industry associations have been formed around the
24 world in Japan, South America and so on, a major
25 function which has emerged has been to liaise with

1 them to ensure that technical information and
2 regulation information, etcetera, is shared with the
3 other associations around the world. And I just
4 participated, for instance, in the Japanese meeting or
5 the Asia Pacific meeting, which was held in Japan,
6 just last month, as an example of the increasing
7 international corporation among the industry
8 associations.
9 Next, please. This slide lists the
10 primary uses of the concentrated, obviously for
11 today's purposes, bovine bone gelatin and, as you see
12 here, this is a list of the major uses for bovine bone
13 gelatin in the United States. It is listed in the
14 standing order of use with photographic still being
15 the largest consumer going on down to food. There's
16 less and less bovine bone gelatin used in food
17 products, by food we mean confectionery and
18 marshmallows or whatever else.
19 It is being, I guess, more replaced there
20 by pigskin porcine gelatins. But anyway, those are
21 the primary uses and, as you see, no matter what the
22 end use, all the gelatins are produced through the
23 same manufacturing processes and my colleagues will be
24 describing those in some detail in a few minutes.
25 Next, please. To give you an idea of the

1 scale of the gelatin business globally, and in
2 particular the bovine part of that production, we have
3 listed here the various theaters, so to speak. Europe
4 is still the biggest gelatin producer. Significantly
5 so with 117,000 tons out of a total of some 270,000
6 tons around the world. Above that, I would have to
7 say, over 25 percent or so is actually bone gelatin.
8 The U.S. in total we make something like 60,000 tons.
9 And again, these are all gelatins, whether bovine or
10 porcine or bovine hide or bovine bone, porcine skin.
11 And as you see, of the 60,000, about
12 17,000 tons is actually bone gelatin. Other covers is
13 Asia Pacific, the Asia Pacific regions and South
14 America, and you see about a third of their gelatin is
15 of bovine bone origin. So totally, bovine bone
16 represents almost 80,000 out of the total of 270,000
17 tons. And to give you an idea again of this
18 international value industry total globally is not
19 that big. It's 1.5 billion dollars equivalent.
20 Next, please. What we tried to do here is
21 to put to ourselves a few questions, the elimination
22 of which, I think, will be helpful to the committee in
23 looking at bovine bone gelatin, in particular, in the
24 U.S. The first question, as you can see is, "Can the
25 U.S. gelatin industry supply total U.S. capsule

1 industry's needs?" The answer is no. And this
2 illustrates how that is the case.
3 As you saw earlier, the U.S. bovine bone
4 gelatin production totals some 17,000 tons, but of
5 that 11,500 are needed for photographic and other non-
6 capsule uses. So you see that that remains, there
7 remains only about 5,500 tons which can be used by the
8 capsule industry, but the total needs, in fact, are
9 10,000 tons, and this means that the shortfall roughly
10 4,500 tons of bovine bone gelatin has to be imported
11 and they come primarily from Europe, also from Japan
12 and India, and immediately derived nevertheless from
13 U.S. bones or from bones from other countries.
14 Next, just continuing that theme, of those
15 4,500 tons of which we need to import, "Can they be
16 derived solely from U.S. bones, even if it's not
17 actually manufactured in the U.S.?" Again, the answer
18 is no. As you see here, the total amount of U.S.
19 bones which are made available to the gelatin business
20 is roughly 130,000 tons and because of its use in
21 photographic production, whether in Europe or in the
22 U.S., and also for manufacturing bovine bone gelatin
23 by other companies outside of the U.S., the amount
24 remaining available for pharmaceutical gelatin
25 production here is only 28,000 tons.

1 The next line which is in bold print
2 illustrates that we need roughly 6 tons of bones to
3 make a ton of gelatin. So that the 10,000 tons of
4 gelatin, which the capsule industry needs, is actually
5 equivalent to 60,000 tons of bovine bones and,
6 consequently, you see the shortfall here is roughly
7 32,000 tons, so to speak, to be able to make all of
8 the capsule industry requirements strictly from U.S.
9 bones. So in other words, the deficit has to be
10 sourced from bone suppliers outside of the United
11 States.
12 Next, so then I apologize, this is a
13 little bit of a busy slide, but the bottom line is
14 that there are, indeed, other sources outside of the
15 United States, but even though the quantity is maybe
16 available for various reasons in terms of
17 surveillance, the inspection procedures and so on,
18 it's not so obvious that the quantities, the tonnages,
19 which are listed in the second line or the second
20 section are, indeed, available and because of the
21 various restrictions and so on, you see, in fact, that
22 the bone and that those numbers diminished to rather
23 smaller numbers.
24 And this really drives to the heart of the
25 matter. This is the crux really of what we want to

1 get at today and my colleagues will be addressing this
2 individually and then in the public comment session
3 later, the question of how we can determine the BSE
4 status adherents and also the question as Dr. Chiu
5 referred to of just when they have to be removed in
6 the gelatin bone process. Again, we'll be traveling
7 to that in some much more detail in later
8 presentations.
9 Next, please. I guess that concludes my
10 presentation, unless there are any questions.
11 CHAIR PRIOLA: Yes, are there any
12 questions for Mr. Masson?
13 DR. MASSON: Thank you.
14 CHAIR PRIOLA: Oh, Dr. Hogan?
15 BOARD MEMBER HOGAN: I have one question.
16 CHAIR PRIOLA: Just a second, Mr. Masson,
17 there's a question.
18 BOARD MEMBER HOGAN: Sorry. I had one
19 question, perhaps it is contained in this information
20 you provided us, which is quite huge. In terms of the
21 amount of gelatin that is derived from Europe, could
22 you tell us something about the country breakdown,
23 that is it's most from the UK, France, Switzerland,
24 etcetera?
25 DR. MASSON: Yes, I think you'll find in

1 the information packet there is a detailed breakdown
2 of the various imports. The consumption in the U.S.,
3 actually the total marketing, is closer to 80,000
4 tons. And as you saw, we make 60,000. There is a net
5 import/export situation. The U.S. does export
6 gelatin, but basically to get to the 80,000 that we
7 need, we need effectively a net import of 20,000 tons.
8 Those 20,000 tons come from quite a
9 variety of countries and, indeed, they are listed in
10 the information packet. We didn't go into the detail
11 of it here, because it's somewhat difficult to
12 differentiate, certainly differentiate country by
13 country. It's a little bit more difficult to
14 differentiate within certain countries whether it is
15 bovine gelatin or porcine gelatin, which is actually
16 being imported. But basically the primary countries
17 who do export into the States would be France,
18 Germany, not so much any more from UK, for obvious
19 reasons, Brazil, Argentina, Japan, India. Those would
20 represent the large majority of the total import
21 picture.
22 And again, the variety of gelatins some of
23 that is bovine bone, for sure, but also a lot of
24 bovine hide gelatin comes, for instance, from South
25 America, and bovine bone also from India. It's quite

1 a variety of types from those principle countries.
2 CHAIR PRIOLA: Dr. Khabbaz?
3 BOARD MEMBER KHABBAZ: Yes, I didn't hear
4 you well and I apologize. When you said in foods
5 increasingly, there's less bovine gelatin and an
6 increased used of porcine gelatin. Was that porcine
7 skin?
8 DR. MASSON: Yes, one can make and,
9 indeed, one does use porcine bones, but the large
10 majority of porcine gelatin made around the world is
11 from porcine skins. And again just to elaborate on
12 that point, the food industry, the present
13 manufacturing process of bone gelatin, which we'll
14 hear much more about in a few minutes, is a very long
15 process. It's a very costly process. Whereas porcine
16 gelatin and hide gelatin, certain portions, is a much
17 sorter process. And economically, therefore, it's
18 much more viable to utilize porcine gelatin, in
19 particular, in the food industry compared to bone, you
20 know.
21 CHAIR PRIOLA: Dr. Bailar?
22 BOARD MEMBER BAILAR: The numbers went by
23 pretty rapidly, but it looked to me like the
24 proportionate shortfall from U.S. production is about
25 the same as the proportionate shortfall when you add

1 production from U.S. bones processed elsewhere. Is
2 that correct? I'm looking at the second and third
3 from the last slides.
4 DR. MASSON: And again, could you just
5 repeat that?
6 BOARD MEMBER BAILAR: Well, in the answer
7 here to question 1, the third from last slide.
8 DR. MASSON: Yes.
9 BOARD MEMBER BAILAR: There was a
10 shortfall of 4,500 tons and a need of 10,000. And in
11 the next one, it was a shortfall of 32,000 tons and a
12 total need of, was it, 60,000, maybe I have misread
13 this. Yes, 60,000. It's about the same proportions,
14 but I understand why these includes other production
15 and the other does not.
16 DR. MASSON: The shortfall with the U.S.,
17 as you see, makes 17,000 tons, that is equivalent to
18 over 100,000 tons of bones, and as we said, basically
19 the cattle industry needs 10,000 tons of gelatin and
20 only half of that effectively is made here in the
21 States. The other half, because of lack of
22 availability of bones and lack of capacity in the
23 States for bovine bone production, has to come from
24 outside of the States, and that's, as you mention,
25 roughly the same proportion. It's almost 50/50. Does

1 that help?
2 BOARD MEMBER BAILAR: If I understand
3 correctly then, adding the U.S. bone processed
4 elsewhere doesn't help much at present?
5 DR. MASSON: Excuse me, adding?
6 BOARD MEMBER BAILAR: Adding gelatin from
7 U.S. bones processed elsewhere does not, at present,
8 help very much.
9 DR. MASSON: No, because again the total
10 demand for U.S. bones, because of the other
11 applications, particularly for photographic and other
12 European and other countries utilization of U.S.
13 bones, they don't always end up as pharmaceutical
14 gelatin. The end up more often as photographic
15 gelatin, so there's just not the amount of U.S. bones
16 going overseas which can come back to the U.S. as
17 pharmaceutical gelatin for capsule production.
18 BOARD MEMBER BAILAR: At what point is the
19 distinction made regarding the ultimate use of the
20 gelatin?
21 DR. MASSON: Regarding what, sir?
22 BOARD MEMBER BAILAR: Regarding the
23 ultimate use of the gelatin. Is it all processed? I
24 thought it was all processed in the same way.
25 DR. MASSON: Well, my colleagues will

1 describe that in a great deal of detail, and it is
2 more or less, yes.
3 CHAIR PRIOLA: And Dr. Wolfe?
4 BOARD MEMBER WOLFE: This is sort of a
5 follow-up on John's question. You mentioned two
6 factors that are rate limited, so to speak, in terms
7 of the use of U.S. bones. One was the capacity,
8 presumably, to convert U.S. bones into gelatin, and
9 secondly, was the unavailability or the shortage of
10 U.S. bones. I can't believe that the second one is
11 really a problem. It is likely that only a small
12 fraction of U.S. bones are currently being exported to
13 other countries for reprocessing. I mean, is that
14 correct or not? I mean, it must be a limitation on
15 production, not a limitation on U.S. bones, and that
16 gets to the issue of why there couldn't be an
17 increase. If the capacity is the problem, why there
18 couldn't be an increased export of U.S. bones to
19 European countries to use them, preferentially, in
20 favor of bones from BSE countries.
21 DR. MASSON: Yeah, your point is well-
22 taken. The problem, however, is that the largest
23 consumer of bovine bone, as you see, is the
24 photographic industry. Out of the 130,000 tons, which
25 is produced in the states, over 100,000 or

1 approximately 100,000 goes to the photographic
2 industry. And by definition, therefore, the remainder
3 simply isn't satisfactory, and we can't drive -- the
4 gelatin industry is at the bottom of the totem pole,
5 so to speak, in terms of creating greater availability
6 of bones. The different industries sell so much bone
7 that's made available to us basically, and there is
8 only so much.
9 BOARD MEMBER WOLFE: Are you saying that
10 the bone either goes to photographic industry or
11 elsewhere and that there isn't, at the present time,
12 bone from U.S. beef that is not being converted into
13 gelatin? I mean, what percentage of the,
14 theoretically, available bone from U.S. beef is, in
15 fact, being converted to some kind of gelatin?
16 Because my question is sort of getting to the issue of
17 whether or not it is possible to divert or not to
18 divert, but just to increase the use of bone from U.S.
19 beef, even though you want to -- you said there's a
20 tug between photographic gelatin and other gelatins if
21 the total amount of bone was available, you could
22 satisfy both of them. So just, specifically, how much
23 of U.S. bone is, in fact, getting converted into some
24 kind of gelatin? Half of it, two thirds of it, all of
25 it? What?

1 DR. MASSON: Well, the bone that is
2 available is being converted. Again, there are only
3 a few bone producers of the major beef players, but
4 only a few of them actually make gelatin bone at some
5 of their facilities. And again, it's supply and
6 demand. We can't. Basically, there's not enough
7 demand from our side that would force them or
8 encourage them, let's say, to produce still more bone.
9 It's that simple.
10 BOARD MEMBER WOLFE: Okay.
11 CHAIR PRIOLA: Dr. Johnson?
12 BOARD MEMBER JOHNSON: Yeah, I may
13 understand the way this is processed. But it seems to
14 me that the ready solution would be that U.S. bone
15 would be used for all consumables, whether they be
16 dietary supplements and then you could use the foreign
17 bone for photographic materials. It's about even.
18 DR. MASSON: On paper that's true, but
19 that's --
20 BOARD MEMBER JOHNSON: That's what I'm
21 looking at.
22 DR. MASSON: Yes. But it's rather
23 simplistic, because again we can't make that
24 determination. It's those industries who make that
25 determination. The photographic industry has

1 determined that they will use bovine bone, and that's
2 their prerogative that we can't influence it.
3 BOARD MEMBER JOHNSON: So a solution would
4 be if we deregulated photographic bovine bone, and
5 that would be a possibility. Does FDA regulate
6 photographic gelatin?
7 DR. MASSON: No.
8 BOARD MEMBER BAILAR: No, they can use
9 whatever they want.
10 DR. MASSON: Yes.
11 BOARD MEMBER JOHNSON: So you could split
12 it up.
13 DR. MASSON: I'm sorry?
14 BOARD MEMBER JOHNSON: If there's no
15 regulation on photographic gelatin, you're subtracting
16 it out to produce all this shortfall, why not make the
17 photographic gelatin from British bones?
18 DR. MASSON: I'm sure some is, but again,
19 we as an industry can't make that determination. It's
20 the photographic people who make that determination.
21 CHAIR PRIOLA: Dr. Bracey?
22 BOARD MEMBER BRACEY: Yes, in the
23 information that you present, the majority of the
24 gelatin is used for photographic purposes. It seems
25 to me that there has been a major move away from film

1 based photography towards digital. Have you seen a
2 reduction in the demand and, in essence, your picture
3 is a static picture, but what does it look like really
4 as far as the demand for photographic gelatin in the
5 future?
6 DR. MASSON: That's a very good question.
7 As you rightly observed, digital photography is here
8 in a big way and will continue to grow. But there is
9 some complimentality between silver halide, the
10 traditional silver halide process, which does utilize
11 photographic gelatin and the digital business. So
12 that the two things, digital is growing certainly at
13 a much more rapid rate, but photographic traditional
14 silver halide photography is still very much en vogue
15 and, indeed, you know, the last photographic
16 companies, Kodak, Fuji and so on still continue to
17 invest quite significantly in the traditional side of
18 the business as well. So the two things, I'm not sure
19 of --
20 BOARD MEMBER BRACEY: Well, I guess, what
21 I'm wondering is over the years the data in terms of
22 total demand has been static or has it been actually
23 declining?
24 DR. MASSON: I would say it is fairly
25 static. There has been a diminution for sure in some

1 sectors of the traditional silver halide, photographic
2 side of the graphic arts, for instance, probably uses
3 any photographic gels any more. That has gone
4 totally, more or less totally, to the digital side.
5 But the traditional film that you or I shoot, the
6 amateur film, medical x-ray and other types of cinema,
7 film photography for movies, those are still the
8 traditional situation, and that demand is still very
9 much there.
10 CHAIR PRIOLA: Yes, is there a question
11 from this side or answer?
12 MR. SCHRIEBER: Thank you, Madam Chairman.
13 I would like to make -- Reinhard Schrieber.
14 CHAIR PRIOLA: Could you identify
15 yourself?
16 MR. SCHRIEBER: From GME, and I would like
17 to make a remark about potential replacement for the
18 photographic industry of domestic bones and imported
19 bones. The following situation is the biggest
20 manufacturer of photographic gelatin is Eastman-Kodak
21 sitting here in the United States. They are forced to
22 use domestic bones, because as a ban on import of
23 bones from out of the U.S. into U.S., because the risk
24 of bringing in bones from maybe BSE risk countries is
25 tremendously high to bring in just in case by the

1 bones BSE into the United States.
2 So gelatin is safe to be imported, but
3 importing bones from other countries, I think, is of
4 high-risk for this community here, so therefore it
5 would really replace and most probably negligible risk
6 with gelatin by a big risk by importing bones,
7 degreased bones from other countries, who therefore is
8 a replacement in this way, I think, is not a good idea
9 for the U.S. On the other hand, I think it is really
10 impossible to force Eastman-Kodak just out of using
11 bones from the U.S. I don't know how their reply
12 would be in this case.
13 And maybe one more question, answer to
14 your question about from which European countries is
15 sourced in Europe has no bone at all coming for the
16 last 20 years from UK, so the European gelatin
17 industry did not source bone from UK. We do not
18 source bone from Ireland. We do not source bone from
19 Switzerland, Portugal, the so-called higher risk
20 countries in Europe. All the bones, proven bones used
21 by the European industry are coming from either
22 Germany, France, Belgium, Netherlands or Austria.
23 These are the source countries. Thank you.
24 SECRETARY FREAS: Because our meetings are
25 being transcribed, we're asking everybody who uses a

1 microphone other than at the table to identify
2 themselves. That was Mr. Schrieber, the chief
3 manufacturing officer of the Gelatin Group.
4 CHAIR PRIOLA: Okay. I think we'll move
5 on to our next speaker. Thank you, Mr. Masson.
6 DR. MASSON: Thank you.
7 CHAIR PRIOLA: Our next speaker is Dr.
8 Dunn, who is going to explain some of the
9 manufacturing processes for gelatin in the U.S. and
10 that might address some of the questions that have
11 arisen.
12 DR. DUNN: I also would like to thank the
13 FDA and the Committee for the opportunity to come in
14 and speak with you today about the practices of the
15 U.S. gelatin manufacturers. My name is again Michael
16 Dunn. I'm currently vice president of Gelita North
17 America, and I also serve as the chairman of the
18 Regulatory Committee for GMIA. As you can tell on
19 this slide, there are two current manufacturers of
20 bone gelatin here in the United States, Eastman
21 Gelatin, who provides to Kodak, they are primarily
22 producing photographic gelatin, and GELITA USA, who is
23 primarily a pharmaceutical producer.
24 When we put those together, though, the
25 majority of this gelatin goes to the photographic

1 applications, although there is a substantial quantity
2 that does go to the pharmaceutical sector as well.
3 The limed share of the gelatin that we produce is
4 limed bone gelatin. We do, however, produce a small
5 amount of what we call Type A or acid bone gelatin,
6 but this is a very small quantity.
7 I also wanted to note that the practices
8 that I'm going to be talking about today, as well as
9 the processes, apply to both GELITA USA as well as
10 Eastman Gelatin. Could I have the next slide? So
11 just to set the overall objectives, they basically are
12 two-fold today. I want to adequately describe for you
13 today what our current sourcing practices are, as well
14 as the processing conditions that we use to
15 manufacture bone gelatin in the United States.
16 I also want to clearly confirm that the
17 bone gelatin processing conditions that we employ here
18 are virtually the same that are currently used in
19 Europe. And more importantly, they meet or exceed the
20 minimum processing requirements that were spelled out
21 in the GME TSE Inactivation Study Protocol. This I
22 want to make clear, because we want to make sure that
23 any of the results, we want to make sure that they are
24 applicable to what we are producing here in the United
25 States, as well as what is being produced in Europe.

1 Could I have the next slide? So when we
2 get to sourcing, in the U.S. degreased gelatin bone is
3 sourced exclusively from USDA inspected beef
4 processing facilities in the United States, and this
5 raw material is derived solely from healthy cattle
6 that have been deemed fit for human consumption based
7 upon both anti and postmortem inspections.
8 Could I have the next slide, please? When
9 it comes to SRMs, the U.S. gelatin bone suppliers have
10 been removing SRMs with the exception of vertebrae
11 since as early as 1998. And right now, limited
12 quantities of vertebrae-free gelatin bone have been
13 available from as early as fall of 2002. Currently,
14 there are no FDA or USDA requirements for the removal
15 of SRMs in the United States. We primarily do the two
16 above bullet points primarily because of EU
17 regulations and we supply a large number of customers
18 that have business in Europe that must comply with
19 those kinds of regulations.
20 Could I have the next slide, please? So
21 let's go on to the process. What I have outlined here
22 is an overview of what happens in a daily gelatin
23 production. The major input, of course, to this is
24 the degreased gel bone. We're on the order of about
25 100,000 pounds of gel bone per a production day. And

1 we have an equivalent amount of hydrochloric acid, so
2 another 100,000 pounds of hydrochloric acid would go
3 into this next. We use at least a half a million
4 gallons of water in the production and, of course,
5 there is a lot of labor and energy that goes into this
6 as well.
7 What I'll be talking about primarily today
8 is what goes on in this blue box here, in terms of the
9 DTL processing conditions. The output we're looking
10 for, of course, is gelatin. On a base of 100,000, you
11 get out about 25,000 pounds of gelatin, and then about
12 50,000 pounds of dicalcium phosphate, which is the
13 primary byproduct of this process.
14 Could I have the next slide? So overall,
15 what we're trying to achieve here, we're starting with
16 the protein we call collagen, which is an extremely
17 fibrous insoluble protein and we're going to transform
18 that into a protein that is fragmented and soluble,
19 but has a variety of very interesting functionalities,
20 which makes gelatin such an interesting business. So
21 there are three major things we are trying to achieve
22 here.
23 Initially, we need to hydrolyze the
24 collagen. We do this by breaking, there is intra and
25 inter molecular cross links between the adjacent

1 chains. We start to break up peptide bonds, so that
2 we're able to water extract this material from the
3 ossein that we're producing. Subsequent to that, we
4 spend a lot of time purifying and concentrating the
5 gelatin. When we do that initial extraction, it's a
6 very dilute solution about 5 percent, so we have to
7 take a lot of water back out of that and then we
8 purify the material from both a chemical, physical and
9 micrological point of view.
10 If I could take the next slide, please?
11 So the incoming gel bone comes to us. It's delivered
12 by a truck or rail car and these are just simply
13 typical characteristics of that material, and we would
14 use the same material to make either the Type B or the
15 Type A gelatin. So the fat content ranges from 1 to
16 2.5 percent. The size of these chips is an 1/8th inch
17 to 5/8th inch. The mineral protein ratio is about 2
18 to 1. And the moisture content is about 6 to 9
19 percent. And in contrast, it's worth mentioning in
20 the EU all of the producers there have their own
21 degreasing facilities, which is different than the way
22 things are done here in the United States. The big
23 meat producers have their own gel bone processing
24 facilities, and they supply us with this finished bone
25 chip.

1 Next slide, please. The first
2 pretreatment step is what we call acidulation. But
3 what is happening here is the demineralization of the
4 bone. This is where all that hydrochloric acid comes
5 into place. What we're trying to achieve here is the
6 production of what we call ossein, which is this
7 demineralized bone material. There's a number of
8 washings, hydrochloric acid washings during this
9 process. We also remove a lot of non-collagen
10 impurities that come in with the raw bone.
11 The concentrations that we're looking at
12 here, maximum, 4 to 6 percent. The way this works is
13 it's a counter-current distribution process. We start
14 out with a dilute hydrochloric acid concentration,
15 that's what the initial bone is exposed to, and it's
16 gradually raised up over this 4 to 5 days. It's a
17 very exothermic reaction, and this is why it takes to
18 long to carry this out to dissolve out all of this
19 material. The typical ambient range as far as
20 temperature after this process is done, the residual
21 acid, is washed out for about a 24 hour period before
22 we go on to the next step, which is on the alkaloid
23 side of things.
24 Could I have the next slide? So if we
25 choose to lime, at this point, this is the breaking

1 point we choose to make either lime bone or acid bone,
2 at this point. In the case of liming, this is a lime
3 pit that you're seeing up there in the picture.
4 Again, we being, this is where we continue to
5 hydrolyze the collagen molecules and there's a lot of
6 washing that goes on here with the refreshing of the
7 lime solution, so we're moving impurities.
8 There is also something important that
9 happens here chemically that is different than porcine
10 gelatin. You hydrolyze away the asparagine and
11 glutamine. You deanimate those and form their
12 respective acids which drops the iso-electric point of
13 that molecule from about 9 down to about 5. So
14 electrically, the porcine and the bovine gelatins are
15 quite different. We use a saturated lime slurry to do
16 this. The pH is approximately 12.5. The liming time
17 is 25 to 70 days that we're tying up this material in
18 production for a long period of time before we can
19 make gelatin out of it. Again, and the temperatures,
20 these lime pits are agitated on a daily basis. We're
21 there to make sure we're getting proper exposure to
22 the alkaline material to the bone chips that are in
23 the pit. And these lime slurries are completely
24 refreshed on a weekly basis.
25 Next slide, please. After that, there is

1 a washing and acidification step. We want to
2 neutralize the excess lime, again remove, wash out
3 additional non-collagen impurities, and we want to
4 adjust the pH of the ossein slurry, so we can prepare
5 it for extraction. So this wash out period under
6 alkaline conditions is 24 to 48 hours under vigorous
7 agitation, temperatures from 45 to 70 degrees. The
8 neutralizing or souring of acids in this case are
9 either hydrochloric or sulfuric acid, and our target
10 pH for this part of the process range between 5 to 7.
11 Could I have the next slide? In lieu of
12 liming or alkaline which is what we do most of the
13 time, we're only talking a few percent of the time we
14 do this process. We can do an acid treatment and
15 produce Type A or acid bone gelatin. So the purpose
16 of this process here is to condition and ready the
17 ossein material for an extraction at a very low pH.
18 In the traditional process, we use a sulfuric acid and
19 we expose the ossein to a pH of about in the range of
20 1 to 2 for about 6 hours, and then we rinse that back
21 to a pH ranging from 2.8 to 3.2. And this is where we
22 will extract the gelatin. This is, I mean, usually pH
23 to extract gelatin. Most gelatin is extracted at much
24 higher, more neutral pH.
25 We also have an alkaline pretreatment

1 option that we're looking at, that some of our
2 customers are looking at, because of all the
3 discussion around sodium hydroxide pretreatment. In
4 this situation, you would do this alkaline
5 pretreatment prior to the ossein treatment. And in
6 this case, you are able to maintain the pH at 13 or
7 greater with sodium hydroxide for a period of three
8 hours.
9 Next slide, please. Okay. Now, we've
10 finished with the pretreatment, whether it be for acid
11 bone gelatin or lime bone gelatin and the rest of this
12 will be common to both of these types of gelatins.
13 Now, we extract the gelatin. This is where we've
14 wetted the gelatin, we've hydrolyzed it, now we're
15 going to actually pull this, extract this out of that
16 ossein particle to produce the gelatin.
17 We use demineralized water. What you're
18 seeing up there is a typical gelatin extractor. We do
19 a series of extractions. I said 4 to 6 depending on
20 the plant and the company, the way they do that. But
21 the initial extracts are done at a lower temperature,
22 and what you will get out is a material that typically
23 has a higher molecular weight, a higher viscosity, a
24 higher bloom strength.
25 As you go to subsequent extracts, that

1 material will become more degraded. It will have a
2 longer profile of treatment with time and temperature.
3 And those ending extracts will conversely have higher
4 collagens, lower molecular rates, lower viscosities
5 and so on and so forth. So the temperature range is
6 from about 120 to 200 as you go through that series of
7 separate gelatin extracts that you are pulling out.
8 The conditioning time for each extraction ranges from
9 1 to 6 hours and it's 4 to 6 extracts.
10 Next slide, please. When that extract
11 comes off, it's a typical, very dilute solution
12 somewhere in the range of about 4 to 6 percent. So
13 you're saying to get to a dry product, we got to pull
14 a lot of water out of here as well. So we have
15 initial filtration, this is a U.S. type filter,
16 vertical leaf type filter. It's precoated with
17 diatomaceous earth and cellulose. And that basically
18 is to give us initial and improvement in the clarity.
19 The solution will also go on to ion exchange. We want
20 to protect these ion exchange collagens.
21 Could I have the next slide, please? So
22 you're looking here at an ion exchange battery. You
23 see three columns in the forefront and three in the
24 background. Those are batteries of cation in that
25 exchange columns. Of course, the objective here is to

1 deionize this material, depending on whether it is
2 pharmaceutical or photographic. It gets more exposure
3 to those columns depending on what is needed.
4 Primarily, the cations we're removing are
5 calcium magnesium and iron. On the anion side, it
6 would depend on the acid that we were souring the
7 material with before we extracted it. And sometimes
8 we use hydrochloric and sometimes sulfuric. So those
9 would be the primary anions that would be removed
10 under those conditions. And the finished product from
11 an ash standpoint would be somewhere between .1 and 1
12 percent, depending on the product that we're making.
13 Could I have the next slide, please? Now,
14 we begin to remove water, and we do this by using
15 evaporative means initially. So we have this 5
16 percent solution that we're going to drive up to a 15
17 to 25 percent concentration. The evaporator you see
18 there in the picture is a triple effect plate and
19 frame type evaporator. The output temperature is not
20 too high. It usually runs about 125 to 130 degrees on
21 the average. Basically, a temperature that will just
22 make sure the gelatin doesn't gel up in the production
23 plant.
24 Could I have the next slide? Then we have
25 another filtration. We heat it again. We've

1 concentrated that material, so there is more
2 particulate becoming apparent, in certain cases, and
3 then there is a chance that you may get some
4 coagulated protein, so we have another clarification
5 step here. The medium we use are exactly the same in
6 the prior filtration cellulose and diatomaceous earth,
7 but we use a plate and frame pressure filter. The
8 viscosity of this solution is increasing now as we
9 move along in the process, and this is what requires
10 a completely different configuration for filtration.
11 Could I have the next slide, please? Then
12 we take the opportunity to adjust the pH, at this
13 point. The final pH targets of the finished product
14 are usually in the range of 5 to 7. At this point,
15 it's usually just a fine adjustment and most typically
16 it's done with sodium hydroxide.
17 Could I have the next slide? Then we do
18 our final concentration with evaporative means.
19 Again, this solution is becoming quite viscus, so
20 we're concentrating our thick, what we call at this
21 point, our thick gelatin liquor. This is an example
22 of a double effect plate and frame type evaporator as
23 well. And the concentration here will be a fairly
24 broad range here from 25 to 50 percent, and this is
25 because, I talked earlier about your initial extracts

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1 are much higher viscosity, so you only will be able to
2 drive those up to about a 25 percent. However, the
3 latter extracts, which have a much lower viscosity,
4 you're able to drive those up to a much higher
5 concentration level, and that's what is done.
6 Next slide, please. Then we go through a
7 sterilization step at the end of the liquid phase.
8 After this, we're going to be going into a more solid
9 mode with the gelatin production, so this is our last
10 opportunity to do something with the liquid phase. So
11 we use direct steam injection. We use a temperature
12 that ranges anywhere from 138 to 149 C for 8 to 16
13 seconds, and this is primarily to ensure the product,
14 hygiene of the product.
15 Next slide, please. Then we're taking
16 another tack here in terms of drying the gelatin.
17 We're beyond evaporative means, so what we do is to
18 increase the surface area, then able to dry this
19 material, we cool it down from about 120 down to about
20 70 degrees where the gelatin actually sets, starts to
21 set, and this is down with a glycol cooled heat
22 exchanger. Then it is extruded out through these
23 perforated heads to form these noodles, which will
24 range in size from under 2 feet long and about an
25 1/8th inch thick, and they are deposited on the front

1 end of a dryer, which is in the next slide.
2 These dryers are typically about 12 feet
3 wide and about 150 feet long. The air quality we use
4 is heated, dehumidified and filtered air. The object
5 is to produce a stable product. It has very low water
6 activity. Typically, it has 10 to 12 discrete zones
7 with different temperatures. There's a gradient that
8 ranges from about 80 to 160 degrees fahrenheit that
9 goes across that entire dryer. It takes about like 2
10 to 3 hours to get through this system, and the final
11 moisture content of the gelatin product is about 10 to
12 12 percent.
13 It's a very touchy process. It's very
14 easy to melt the gelatin. If you try to dry it too
15 fast, you know, with too much water, the melting point
16 is lower and it is going to melt down or you can get
17 case hardening. It's a very delicate process drying
18 this gelatin effectively.
19 Next slide, please. Then we do a milling
20 after the drying and our size is typically 8 mesh.
21 That's our kind of working mesh size. We can do a
22 variety of mesh sizes in the finished product, but
23 most of our intermediate products we're producing
24 these intermediate extracts that we use to do our
25 final finished blending, and it's typically about 8

1 mesh.
2 Next slide, please. So as these
3 individual extracts, whether it be 4 or 6, come off
4 there, they are separated on the dryer as discrete
5 extracts. Those individual extracts from daily
6 production are individually blended to make sure that
7 there is no lack of homogeneity as that material is
8 processed across that dryer. So we blend those with
9 homogeneity. We sample those materials, as
10 intermediate product, and those that go in the dryers
11 are weighed and go into storage as intermediate
12 product for future blending and mixing.
13 Next slide, please. So there is our
14 inventory that we're building up with our daily
15 production, and then based on the specifications of
16 our customers, we build mixes and we formulate mixes
17 with these individual extracts that we have been
18 producing. These are much larger blends. Some of
19 these are 10, 20, 40,000 pound mixes, so now we have
20 a high capacity blender that allows us to put those
21 together.
22 Many times we'll make a much smaller small
23 scale mix to make sure that we can blend it properly,
24 particularly if it's a new product. We can hit the
25 specification before we go to the large scale blend.

1 So sometimes there is a series of analysis that we've
2 done it two or three times before we finish off the
3 finished product.
4 Next slide, please. And then we provide
5 that product once we are ensured that it meets the
6 specifications of customers. We'll package that up
7 using drums, FIBCs or small bags and then it is off to
8 the customer.
9 I hope that has given you a quick -- I had
10 to go through that rapidly. There is a lot of
11 information to cover there, but you've got that in
12 your handouts there. So I hope that was useful and I
13 would be glad to entertain any questions you have.
14 And I also would like to invite you to come out to see
15 our facility in Sioux City, Iowa if you would like to
16 see first hand how we make gelatin.
17 CHAIR PRIOLA: Yes, Dr. Bracey?
18 BOARD MEMBER BRACEY: Yes, I have one
19 question. You said in the cation exchange process
20 that you treat the product in a different manner
21 depending upon the end use, i.e., photographic versus
22 other. So, in essence, that suggests that there is
23 the potential for control.
24 DR. DUNN: That's right. That's right.
25 I mean, there are certain types of food products where

1 you may not go through the columns at all. I mean, it
2 depends on the ash content. Typically, the ash if it
3 was unprocessed, it could be as high as 2 percent,
4 okay. In some cases, there would be no need. And it
5 would get very sophisticated with the photographic
6 realm whether you are interested in anions and
7 cations, you go through a cation and bypass an anion
8 or you may go through a secondary column.
9 You know, we have a battery with three
10 columns of each type. Usually, one is a lead column,
11 lag column and then there is a regenerate one under
12 regeneration. So there is a variety of ways to go
13 through that ion exchange system, depending on what
14 the specifications of the customer are. You might
15 have a food customer who says well, ash is less than
16 2 or you might have a photo customer and it has got to
17 be between .1 and 2.5 or .1 and .25 or something like
18 this. There is all kinds of variations on the thing
19 in terms of exposure to ion exchange.
20 CHAIR PRIOLA: Dr. Bailar?
21 BOARD MEMBER BAILAR: I understand from
22 Dr. Chiu that it is the processors who are responsible
23 for the safety of supplies. How is that monitored or
24 enforced here and abroad?
25 DR. DUNN: You're talking about the supply

1 of our gel bone?
2 BOARD MEMBER BAILAR: Right.
3 DR. DUNN: Okay. We audit our suppliers.
4 One of the things that makes it a little bit easier
5 here in the States is we only have a few. We
6 basically have -- it depends on the company. Between
7 the two companies, I think, we have five or at most
8 six different suppliers. So it's not an unmanageable
9 deal to go in and audit these customers on a regular
10 basis. We also know that USDA is in these plants.
11 They help us with this. As a partnership, they are in
12 there auditing all the time.
13 For example, when we worked with the USDA
14 because of these European regulations to start taking
15 our SRMs, back in 1998, they worked with us to do
16 that, to go in and validate those procedures and so
17 on. So we have an ongoing program in that respect and
18 we work with the USDA sometimes to do various things
19 as well.
20 BOARD MEMBER BAILAR: What about foreign
21 supplies?
22 DR. DUNN: All of our suppliers here in
23 the United States, everything we source is here in the
24 United States right now.
25 CHAIR PRIOLA: Can you remind me, you said

1 there were Type B and Type A --
2 DR. DUNN: That's right.
3 CHAIR PRIOLA: -- process and the Type A
4 is acid?
5 DR. DUNN: Type A is the acid. Type B
6 means base.
7 CHAIR PRIOLA: Right. And why do you
8 choose one of those others?
9 DR. DUNN: Like I said, we do very little
10 Type A. I mean, very little. We're talking probably
11 less than a couple percent, something like 2 to 3
12 percent, and that's all directed to the pharmaceutical
13 capsule industry, and there are reasons for that.
14 Because of the way we process this material, the ratio
15 of viscosity bloom and the ratio of viscosity to
16 concentration is very different. We can acquire a
17 very low viscosity concentration ratio with this
18 process for acid bone.
19 And sometimes those customers who make the
20 capsules require that they have a higher
21 concentration. And the limit usually is viscosity.
22 So if they can get a gelatin that has a lower
23 viscosity to concentration ratio, that allows them to
24 bring more gelatin into that capsule, and sometimes in
25 the soft gel, it depends on the drug fill and what is

1 going on there, that can be very important. So it's
2 very important for a number of applications in the
3 soft gel area.
4 CHAIR PRIOLA: All right. So even though
5 it's a small percent of the time you do this process,
6 most of it goes to the pharmaceutical industry?
7 DR. DUNN: That's right.
8 CHAIR PRIOLA: Then the sodium hydroxide
9 option, the base treatment, you said that's under
10 review. Is that to see how that might effect --
11 DR. DUNN: That's right. That's under
12 review for acid bone. The most important thing it's
13 under review by our customers, and they are currently
14 evaluating that to see if there is not any other
15 shortcomings of the fact that the sodium is there as
16 opposed to the calcium from the lime.
17 CHAIR PRIOLA: Does it seem to change the
18 end product at all?
19 DR. DUNN: From our prospective, it
20 doesn't, but that's why we're relying on the capsule
21 manufacturers to do their full evaluation and that's
22 what we're looking for. Okay. So we can do it. It's
23 easy for us to do. It's not a problem for us to do
24 that.
25 CHAIR PRIOLA: Dr. Khabbaz?

1 BOARD MEMBER KHABBAZ: Yeah, I have a
2 question regarding the bovine bone sourcing practices.
3 You said since 1998, you have been removing the
4 specified risk materials, except for vertebrae.
5 DR. DUNN: Yes.
6 BOARD MEMBER KHABBAZ: Why that exception
7 and is it still practiced?
8 DR. DUNN: That's a very difficult thing
9 to do, and there is really up until recent times there
10 has been no requirement. There are EU regulations now
11 developing and that's why there is concern there that
12 that may be a requirement coming into place as early
13 as the end of this year. We're not sure how this is
14 going to roll out, so we're looking at this
15 strategically. Right now, there is not a requirement,
16 but there is a big hurdle there in terms of industry's
17 ability to do this.
18 This will cost us more money. It will
19 reduce the amount of bone available. Right now, if
20 you take the vertebrae and take it somewhere else, you
21 reduce the quantity right there by 25 to 50 percent.
22 And then there will be certain facilities that will
23 just not be able to do this with the equipment they
24 have. They won't be able to make this change without
25 investing new capital. But anyway, the prices we are

1 seeing now, you can get this material, small masses of
2 this material now, but it is going to cost you 50 to
3 100 percent more than the traditional. So, I mean,
4 nobody wants to go there unless we have to. It's
5 going to be very costly for us, our suppliers and our
6 customers.
7 CHAIR PRIOLA: Okay. Thank you very much,
8 Dr. Dunn.
9 DR. DUNN: Thank you.
10 CHAIR PRIOLA: I think we'll move on to
11 the next speaker. It will be Mr. Schrieber, who will
12 describe the European manufacturing processes for
13 gelatin.
14 MR. SCHRIEBER: First slide, please. I
15 would like to thank you, Dr. Priola, this Committee
16 and the FDA for the opportunity of presenting on
17 behalf of the Gelatin Manufacturers Association, GME.
18 Again, details about raw materials sourcing and the
19 bone gelatin manufacturing practices in Europe. My
20 name is Reinhard Schrieber. I'm the chief
21 manufacturing officer operating GELITA Gelatin Group.
22 I'm 36 years in the gelatin business, and I have
23 served at European Gelatin Association for many years
24 as president, chairman of the regulatory committee and
25 the chairman of our BSE Steering Committee.

1 After my American colleague, Mr. Dunn, has
2 already substantially presented the details of the
3 bone gelatin manufacturing process, I would like to go
4 only relatively shortly into this issue. The
5 manufacturing processes in general and although the
6 bone gelatin manufacturing processes in particular are
7 very similar to each other, not only in the U.S. and
8 Europe but all over the world. The main differences
9 which can be noticed between the continents are
10 related to the safety status of the raw material and
11 the sourcing systems in place.
12 This is why I like to focus more on these
13 topics, whereas I would like to try as well to connect
14 the connections and the conditions of our study to
15 those existing in reality.
16 Next slide, please. GME members have
17 taken several voluntary steps to ensure the safety of
18 the raw materials. Long before the emergence of BSE,
19 the European gelatin industry has decided to use, and
20 this applies for all types of raw materials, only raw
21 material coming from healthy slaughtered animals and
22 released for human consumption, regardless of whether
23 this was mandatory or not in different member states.
24 So we don't use any materials from fallen or sick
25 animals.

1 So traditionally, no material from fallen
2 animals have been used by European manufacturers. The
3 three bones gelatin manufactures in Europe have never
4 used UK bones, but when BSE in the UK became evident,
5 they confirmed immediately in writing not to use UK
6 bones. After the condition of BSE to humans was
7 detected, the GME members committed themselves to stop
8 the use of skull bones, the target which was reached
9 in 1997. This was further followed by the complete
10 removal of spinal cord by European meat packers only
11 on request of the European gelatin industry.
12 In parallel, our industry started to
13 replace European bones to a certain extent by imported
14 bone chips, mainly from the United States, but also
15 from other countries outside Europe. In 1999, the
16 European gelatin industry was able to convince its
17 suppliers to remove vertebrae from bovine bones of all
18 ages, which again was more than European law required.
19 Next slide, please. As I stated before,
20 on top of our European sourcing of our demand for
21 bovine bones can only be covered with additional
22 imports from different countries. So we always force
23 our suppliers in GBR II countries to voluntarily take
24 measures in order to increase the safety of our raw
25 materials. GBR II country means that there are so far

1 no BSE case detected and the European has assessed
2 that it is unlikely that there will be a case, but it
3 cannot be excluded.
4 The U.S. is and Canada has been until
5 recently GBR II countries. Together with our American
6 colleagues, we implemented the removal of spinal cord,
7 also in the U.S., and one year before we succeeded in
8 doing so in Europe, we had forced our suppliers in
9 India, Pakistan, Nigeria to remove the vertebrae as a
10 precautionary measure.
11 Next slide, please. Most of the measures
12 which we had already implemented became mandatory by
13 regulation in Europe some years later. On top came
14 the postmortem rapid testing of all cattle older than
15 30 months. Furthermore, the removal of vertebrae as
16 requested now by law only for animals older than 12
17 months, but again in the bones we use in Europe, there
18 are no vertebrae in at all. So in practice, the
19 vertebrae is removed from all cattle in the European
20 Union if the bones are intended to be supplied to the
21 gelatin industry.
22 I assume that you are aware of all those
23 regulations presented to you, I think, by Dr. David
24 Asher in February of this year. With gelatin
25 regulations, the EU fixed raw material sourcing

1 conditions and certain safety relevant procedures to
2 all kinds of food grade gelatin. This has been
3 presented to this Committee two years ago by my
4 colleague, Dr. Scheigas. Those requirements are in
5 line with the new study conditions, and our regular
6 intervals controlled by public veterinarians
7 responsible for the supervision of our plants,
8 although the FDA has made audits to the gelatin bone
9 manufacturers in Europe two years ago, they went to
10 all plants.
11 Next slide, please. Because of the steps
12 taken by the industry, there was always only a very
13 little chance that BSE infectivity could be present in
14 the raw materials used to produce bovine-origin. To
15 date, due to additional more recently implemented
16 controls like the postmortem BSE testing and the
17 careful removal of all SRM, it is almost impossible
18 for highly infected material to enter our supply
19 chain.
20 Next slide, please. As with any process
21 and systems, there is a certain possibility of error.
22 What could happen, for example, animals with very low
23 infectivity might not be detected by the rapid BSE
24 test. But they are considered today as to posting no
25 risk to human health. The surveillance systems in

1 place might not be adequate in all countries. The
2 removal of SRM may not be done perfectly. The
3 infectivity of bone marrow has not been finally
4 clarified. Based on our experience, we believe that
5 those risks are low, but they are not negligible.
6 They will be quantified by the Scientific Steering
7 Committee of the European Union and then used in the
8 coagulation of the quantitative risk assessment, which
9 is currently under development.
10 Next slide, please. Last year, more than
11 9 million normal slaughtered animals were tested on
12 BSE within the whole European Union, including the UK.
13 And 287 positive cases were found, which gives a ratio
14 of 1 to 50,000. But our tests which had been done and
15 our study has assumed that all animals used were
16 clinically infective. Supposing that the removal of
17 SRM is not effected perfectly and that those
18 impurities may not be detected by the gelatin industry
19 when inspecting the incoming fresh bones, some might
20 enter the process. Again, our tests and our study
21 have assumed that the bones from all animals contained
22 the food quantity of infective spinal cord and dorsal
23 root ganglia. Well, this gives a huge safety margin
24 between the study conditions and reality.
25 Next slide, please. Here again, the major

1 production steps applied during the commercial and the
2 study manufacturing processes, most of them have
3 already been described by Dr. Dunn. All plants in
4 Europe are ISO 9000 certified for the quality
5 management and they apply the HACCP principles. The
6 combination of those is about equivalent to GMP. FDA
7 audits have been successfully conducted in all
8 European bone gelatin operations two years ago. And
9 a further round of audits is scheduled for the end of
10 August and early September this year.
11 It has to be noted that SGS and
12 independent institute specialized in quality
13 certification carried out a validation audit. And
14 each of the bone gelatin plants of GME in Europe and
15 there are no known GME bone gelatin plants in Europe,
16 and by these inspections all processed parameters of
17 our study design have been validated against minimum
18 production conditions in place in those plants.
19 Just to clarify what this means, minimum
20 conditions. In certain plants, for example, a higher
21 concentration of the hydrochloric acid or a longer
22 liming time might be applied by one or the other
23 manufacturer compared to the conditions of this study.
24 But we used in our study the minimum conditions
25 applied at least by all manufacturers.

1 Next slide, please. One of the
2 differences in Europe compared with the rest of the
3 world is the fact that in Europe bone gelatin
4 manufacturers have their own bone degreasing plants.
5 In other countries, like the U.S., degreasing is part
6 of the meat packers work. In the Far East, for
7 example, it is effected by independent specialized
8 companies. As mentioned before, only bones from
9 healthy slaughtered animals released for human
10 consumption following audit and postmortem inspection
11 are collected from the meat processors, who do then
12 later the deboning of the carcasses.
13 In the U.S., slaughtering and deboning is
14 done normally at the same premises. In Europe, we
15 have very often different locations. So this means
16 that the carcasses of the animals are transported to
17 a sausage manufacturer, to a meat packer at a
18 different place and during this transport, the bones
19 are still with the carcass. Only the SRM, the spinal
20 cord, the heads are gone, spinal cord is out, but the
21 bones are still with the meat.
22 The incoming uncrushed bones are then
23 inspected by the gelatin industry on sorting belts for
24 extraneous materials, including potential SRM
25 contamination. Then the bones are crushed to small

1 chips of about 5/8ths of an inch, this fingernail size.
2 Then the bones -- this means after crushing that we
3 have a big surface. And for example, with the hollow
4 long bones the inside would as well become an outside.
5 These small bone particles are then
6 degreased by hot water in a continuous flow process at
7 approximately 185 degree fahrenheit of an average
8 period of about 20 minutes in equipment with high
9 education. This mix of water, temperature and
10 movement separates fat and soft tissue from the solid
11 bone particles. The little ones are then separated by
12 sieves and cyclones, dried with hot air, but the
13 surface temperature of the bone particles will stay
14 below 150 degrees fahrenheit to avoid degradation.
15 Then they are sieved to remove fine particles and
16 stored in silos.
17 Next slide, please. Demineralization to
18 remove the phosphates from the bones is carried out at
19 the same conditions like in the U.S. in a conduct
20 current system. The total treatment is about 4 days
21 with hydrochloric acid of 4 percent. The remaining
22 protein matrix of the bones is called ossein.
23 Next slide, please. To cut the cross
24 veins of the collagen acid or alkaline can be applied.
25 This was addressed just before. For a small portion

1 of the total bovine bone gelatin production, it is
2 about 2 to 3 percent for special pharmaceutical soft
3 gel capsules. The ossein is treated again for 24
4 hours with sulfuric acid at the low pH and after some
5 washes, the gelatin can be extracted at a pH between
6 2 and 3.
7 So standard bovine bone gelatin is
8 normally extracted at a pH between 6 and 7. And the
9 ossein is treated before the saturated or over
10 saturated lime solution for at least 20 days. As you
11 have heard, the pH of this lime solution, which is
12 replaced several times during the process, is around
13 pH 12.5.
14 Next slide, please. To make sure that
15 acid bone will be as safe as lime bone, our industry
16 looked into an alternative process which would include
17 an alkaline pretreatment, but without working the
18 special physical and chemical properties of this
19 pharmaceutical as in bone gelatin. Based on the
20 knowledge that after the bones are crushed potential
21 infectivity would sit on the surface of the bones and
22 not inside the bone matrix, we assumed that a short
23 time treatment of about 2 hours with .3 molar sodium
24 hydroxide solution should be enough to inactivate
25 infectivity if this pH is kept at 13 for this time.

1 Our study results have shown that this
2 treatment is very effective. But our study has also
3 shown that gelatin made by the traditional acid bone
4 process did not show any detectable remaining
5 infectivity, which means there is a demand for this
6 type of gelatin is still very rare. You've heard that
7 we are depending, of course, on our suppliers to do it
8 or not to do it.
9 Next slide, please. During extraction of
10 the pretreated raw material, several single extracts
11 are collected, each with different physical properties
12 due to an ongoing hydrolysis during the extraction.
13 It has to be stated that due to the different
14 requirements of the gelatin using industry, quite
15 often photographic, pharmaceutical and food grade
16 gelatins manufactured from the same raw material batch
17 in sequence. Also, Eastman-Kodak is manufacturing
18 some pharmaceutical and some food grade gelatin.
19 This means that all gelatin of one
20 production day, including the photographic gelatin,
21 have to comply with the regulatory requirements for
22 food and pharma. When talking about food and pharma,
23 one has to keep in mind, as well, that the same
24 capsules might be filled today with nutritional
25 products, being food, and tomorrow with Rx drugs.

1 Next slide, please. For further
2 clarification, the diluted gelatin solution is
3 filtered by different types of equipment and filter
4 media in the ossein and ion-exchange columns and
5 concentrated in the apparatus.
6 Next slide, please. So final concentrated
7 gelatin solution is sterilized by direct steam
8 injection. The temperature is at 4 bar. The pressure
9 in the liquid phase, which is very important, is a
10 minimum of 280 degree fahrenheit and the temperature
11 stays for at least 4 seconds.
12 Next slide, please. Finally, the
13 sterilized gelatin solution is chilled to set and then
14 dried with purified and conditioned air on belt
15 dryers. Each production batch, which is a single
16 extract, is then tested on physical, chemical and
17 bacteriological properties. According to customer
18 specification, different production batches are then
19 dry blended. The final blends are again tested under
20 compliance with regulatory and customer requirements
21 and then released for shipment. These are the common
22 processes applied by the European industry.
23 Next slide, please. There is one special
24 process which is done by only one company in Europe to
25 manufacture gelatin with low gelling strength for

1 limited applications. The degreasing is done of the
2 bones in the common way, but then the bone chips are
3 autoclaved for at least 20 minutes under 3 bar
4 pressure and 270 degree fahrenheit. After the
5 autoclaving, bone chips are rinsed with salt water.
6 A certain quantity of gelatin goes into solution.
7 After this gelatin solution is taken out,
8 autoclaving at lower temperature and shorter time is
9 repeated several times. Then these different extracts
10 are collected, flocculated, ion-exchanged and
11 evaporated, drying, testing, blending, retesting and
12 shipping is effected, like with all other gelatins.
13 Low gelling strengths, the gelatin is used only for
14 certain applications, and the Committee members might
15 remember that two years ago at this meeting, we
16 already explained that the main application is a
17 confectionery licorice, although this process has been
18 successfully simulated during our study.
19 Next slide, please. What are the
20 conclusions which we have drawn from this review
21 presented here? So commercial mineral manufacturing
22 conditions are reflected by the GME study conditions.
23 The GME plants and process parameters have been
24 validated for conformity against the study design.
25 The inactivation results of the study, which will be

1 presented next, are therefore fully applicable to the
2 practical gelatin manufacturing processes. The study
3 demonstrates the ability of the gelatin manufacturing
4 process to remove and inactivate infectivity even
5 under conditions in which raw material contain
6 unrealistically high infectivity levels.
7 Last slide, please. So safety of European
8 bone bovine gelatin is established on two principles.
9 The safety of the raw material as required by GME
10 practices and EU law and the safety of our
11 manufacturing processes as demonstrated by the GME
12 study. The Scientific Steering Committee of the
13 European Union has concluded based on all these
14 principles, in it's opinion, on the safety of gelatin
15 that the risk is close to zero.
16 Madam Chairman, Committee, that concludes
17 my presentation. I would like to thank you and the
18 Committee for your attention. Thank you.
19 CHAIR PRIOLA: Okay. Thank you, Mr.
20 Schrieber. Are there any questions? Okay. Thank you
21 very much. Our schedule says there is a break, I
22 believe, after Mr. Schrieber, so we can adjourn and
23 return at 10:00, so that's about 15 minutes from now.
24 All right. Thank you.
25 (Whereupon, at 9:42 a.m. a recess until

1 10:03 a.m.)
2 SECRETARY FREAS: We're going to go ahead
3 and resume the meeting.
4 CHAIR PRIOLA: Okay. I would like to go
5 ahead and get started. Dr. Hogan had a question for
6 our last speaker, Dr. Schrieber, that he would like
7 the Committee to hear the answer to. So, Dr. Hogan,
8 do you want to?
9 BOARD MEMBER HOGAN: Mr. Schrieber, I
10 asked just after our last talk about how the meat
11 processors were audited, in terms of providing safety
12 of the raw materials to the gelatin manufacturers.
13 Could you address that, Mr. Schrieber, please?
14 MR. SCHRIEBER: Surely. The standard
15 procedure in Europe is that in every slaughter house,
16 every meat packing operation there is a public vet
17 present all time, every day as long as this operation
18 works to supervise that regulation is followed,
19 removal of SRM is done and so on. And besides this,
20 the gelatin manufacturer are auditing their suppliers
21 on a regular basis, normally once a month or every two
22 months, again inspecting as well the commercial
23 documents about where the animals have been sourced,
24 because commercial document which is required as well
25 by law. So there's a double-fold. But the main thing

1 is that the public vet is present all day, all the
2 time. Thank you.
3 CHAIR PRIOLA: Okay. Thank you, Mr.
4 Schrieber. We'll go on to our first speaker for this
5 later morning session. That's Dr. Robert Somerville,
6 who is going to discuss the GME validation studies on
7 bone gelatin.
8 DR. SOMERVILLE: Okay. Thank you, Madam
9 Chairman. It's a pleasure to be back in the USA where
10 I've spent quite a few happy years working a couple of
11 decades ago. My task is to describe to you the actual
12 validation studies that were performed in three labs
13 actually over several years. There were several
14 people involved and I want to mention them. First, Ad
15 Grobben is perhaps the most important one of them all,
16 because he, as an employee of gelatin, which was a
17 member of GME, actually performed or was participating
18 in all three studies in Edinburgh, in Holland and here
19 in the USA in Baltimore.
20 Phil Steele, actually I should say that,
21 I know a consultant to GME and is present in the
22 audience and I hope will assist in any different
23 questions you might ask me later on. Phil Steele is
24 a technician in my group and he assisted at not only
25 in the work he did in Edinburgh, but also in Holland

1 to assist in the experiments there.
2 David Taylor was my predecessor in running
3 the inactivation group, and he initiated the studies
4 that we're about to describe and collaborated in
5 setting up the whole thing. He again is here in the
6 audience. I inherited the work from David and
7 responsibility for the work when David retired in
8 2000, so it's my duty to report the results, but all
9 the hard work was done before that.
10 The work I'm specifically going to
11 concentrate is on the Neuropathogenesis Unit, which is
12 part of the Institute for Animal Health in Edinburgh.
13 It was funded by GME with further support from the
14 European Union. I should also say that at the end of
15 my presentation, I suggested that Bob Rohwer, who
16 performed the Baltimore studies, spend a few minutes
17 describing the work that was done in Baltimore.
18 The next slide, please. I thought it
19 would be helpful to describe the basic mechanisms of
20 TSE inactivation first, and there are three ways in
21 which inactivation or removal can take place. The
22 first is through some form of destruction through
23 combustion, incineration, oxidation with hypochlorite,
24 hydrolysis of extreme pHs or with very high
25 concentrations of highly effected proteases and

1 radiation can have an affect at very high doses.
2 Next section, please. What possibly
3 concerns us mainly today is denaturation type of
4 processes where materials hydrated, in particular,
5 will have a degree of inactivation effect and exposure
6 to chemicals, such as strong detergents or chaotropes,
7 can also have an effect.
8 Next. And we have to look at treatment
9 variables. There are several biological parameters
10 that we must consider. The strain of the TSE agent is
11 particularly important and I will illustrate that in
12 a couple of slides time. The PrP genotype may well be
13 important, and we have to consider that. The tissue
14 and the state in which the tissue is presented in the
15 experiment are also important. We have to consider
16 physicochemical parameters such as heat temperature,
17 pH and the kind of chemicals that one uses. And
18 finally, the dynamics and kinetics of the reaction
19 have to be considered, the time, concentration of any
20 chemicals involved and the temperature are
21 particularly critical.
22 Next. Okay. This shows a slide of some
23 data that was originally published in 1983 by
24 Kimberlin, et al, where TSE infectivity from two TSE
25 strains was heated for various lengths of time shown

1 on the axis. On the Y axis is the titre that was
2 recovered after these treatments. Two strains were
3 used, as I say the 22A strains and the 139A strain,
4 and you can see that there is a lot of rapid reduction
5 in the amount of infectivity present, first. Then a
6 plateau. So the reaction is biphasic with respect to
7 time, and there is little effect of time after initial
8 exposure.
9 The second point to notice is that was a
10 strain difference, so the 22A strain on this
11 particular example is much more resistent to an
12 activation than the 139A strain.
13 Next. Now, in this slide, we're looking
14 at what happens when we heat at a constant time, 30
15 minutes, with a range of temperatures, and what we can
16 see here is that there is little reduction in
17 infectivity to start off with until we reach an
18 inflection point, and then the amount of infectivity
19 drops rather rapidly, and that happens for both the
20 TSE strains that we're looking at here. But you can
21 see that the inflection point for these two strains
22 differs, so that for 22C, it's rather thermolabile,
23 which might be a surprise to some. In fact, this
24 temperature which starts to inactivate is only about
25 70 to 75 degrees centigrade.

1 With 22A it's higher, about 97 degrees.
2 But we haven't specifically done experiments
3 comparable to this BSE or BSE derived strains,
4 although I'm hoping to do them in the near future.
5 But from the data that we have available, we think
6 that BSE derived strains are even more resistent to
7 inactivation than the 22A strain here in red, which is
8 the more thermostable of the ones we have seen. So we
9 can say the inactivation process is biphasic with
10 respect to temperature and dependent on temperature.
11 TSE strain, and I mentioned the hydration state, and
12 I'll come on to that in one moment.
13 Next slide. Okay. This slide shows the
14 effect of hitting again at 126 degrees centigrade for
15 30 minutes autoclave, three strains of TSE, and you
16 can see with the 22C strain that all infectivity shown
17 in red has been destroyed. The blue shows the
18 starting titres. The two different blue bands are
19 indicative of two different PrP genotypes that the TSE
20 strains were passaged in, and there is no effective
21 PrP genotype in this experiment available.
22 With ME7, we cover both the types, a
23 little infectivity, but with 301V, we cover a lot
24 more. Now, 301V is important to the rest of this
25 talk. 301V is the most thermostable TSE strain that

1 has been derived from the passage of BSE through a
2 particular strain of mice, the VM strain of mice. And
3 it has certain advantages to these studies. Notably,
4 it is very high thermostability, and that makes it a
5 greater challenge to the studies that we are
6 performing.
7 On the right hand side of the panel, you
8 can see a different experiment where material was
9 heated in a dry oven to 200 degrees centigrade for
10 either 20 minutes or 60 minutes. And I think the
11 contrast between what happened in the autoclave and
12 the dry oven is really quite remarkable. We get much
13 less reduction in infectivity and we've lost our
14 strain differentiation. So there's no strain
15 difference in the results. And also material survives
16 the dry oven much better than it does in the
17 autoclave. So that emphasized the point about
18 hydration status. I think if we dry out infectivity,
19 we make it much more resistent to inactivation.
20 Can I have the next one? Okay. This is
21 an experiment where we have combined temperature
22 treatments with a range of pHs. I don't suppose you
23 can read this, but each line represents a different pH
24 from pH 7 up to pH 12 with three strains of TSE again,
25 301V, ME7 and 22C. And the point is to say that with

1 301V, in particular, we got very little reduction in
2 the amount of infectivity up to 100 degrees.
3 Certainly up to pH of 11.
4 We didn't measure what happened at pHs
5 greater than 11, whether we were getting any reduction
6 infectivity at pH 12 up to 100 degrees, but at 60 and
7 below there was very little reduction in the amount of
8 infectivity recovered there. You do start to see, in
9 effect, that pH 12 with the more thermolabile strains
10 ME7 and 22C. So the suggestion is that high pH acts
11 synergistically with temperature when TSEs are
12 inactivated.
13 Can I have the next slide, please? So on
14 the left you can see a list of the things that I have
15 been showing on all previous, three or four slides,
16 and results and conclusions. Thermostability is an
17 intrinsic property of TSE agents developed to kinetic
18 mother which I'm not going into today, and so forget
19 about the rest. Thank you.
20 Next slide. Okay. I want to move on now
21 to reduction of risk of TSE infectivity in gelatin.
22 The challenges that we face, there is very high
23 resistent to inactivation, and the resistance
24 increases on drying up infectivity. There are several
25 available approaches. We can remove by filtration,

1 for example. We can denature with heat and high pH or
2 we can use at very high pH, we can get hydrolysis of
3 infectivity.
4 Looking specifically at the risk reduction
5 steps that are available in gelatin manufacturing, the
6 sourcing of bones, which Mr. Schrieber has just
7 described, is important as practices in precleaning
8 the raw materials. I'm not going to discuss this.
9 The standard gelatin extraction methods are thought,
10 were thought to be effective, and that is what the
11 valid study of it we've been involved in is designed
12 to test. And then the sterilization steps are steps
13 which may specifically move TSE infectivity and, of
14 course, other contaminants.
15 Next slide. Now, this slide shows the
16 results from the very first studies that were
17 performed in the gelatin manufacturing process. What
18 was done by Inveresk was to take any 7 grain
19 homogenate and look at two components of the process,
20 either treating with hydrochloric acid, the liming
21 step or the combination of the two. The reduction in
22 titre after exposure to the hydrochloric acid was
23 about 1 log, 1.2 was measured. So that's 10-fold
24 roughly.
25 Exposure to lime for 20, 45 or 60 days

1 resulted in a reduction in titre of about 2 to 2.3
2 logs. And you can see that even after 60 days, these
3 values are very similar. So there was a small
4 reduction of about 100-fold, but the time of exposure
5 had new extra effects. And the combined treatment
6 results in the reduction of nearly 3 logs, but you can
7 see that adding these two values together does not
8 come to 2.8. So there isn't complimentary effect, but
9 the treatments are not completely out of it.
10 Can you give me that slide, please? So
11 there is a reduction in infectivity titre measured by
12 the acid and alkali in combined treatment of any 7
13 homogenate. The combined treatment is more effective
14 than either single treatment, but they are not titre,
15 and time of exposure to costs in hydroxide does not
16 effect infectivity titre. And these processes were
17 not representative of the actual process involved in
18 the plant.
19 There is another study by Manske, et al,
20 which showed that there was removal of proteins under
21 industrial degreasing conditions. These initial
22 studies led to the desire for more systematic studies
23 to be performed.
24 Next slide, please. As I've already
25 indicated, there was several experiments performed.

1 In Edinburgh we performed four experiments, two
2 alkaline treatments using two TSE strains, the 301V
3 strain, which I have described, also the 263K strain,
4 which is a hamster-facade strain, which we believe is
5 reasonably thermostable, but may not be quite as
6 thermostable as 301V.
7 We also looked at an acid process and we
8 tested the addition of an NaOH treatment in the acid
9 process. Mr. Schrieber has described the Dutch heat
10 and pressure method and an experiment was performed in
11 the Netherlands to look at that process. And as I
12 say, Bob Rohwer will describe the sterilization
13 filtration experiments later.
14 Next slide. Okay. The rational of the
15 experimental design. The TSE source is a high titre
16 BSE derived model. It's thermostable. It's readily
17 assayed in experimental mice. We feel that the total
18 titre is a likely BSE contamination event during
19 industrial processing the gelatin, as Mr. Schrieber
20 has already suggested. Short incubation periods, but
21 we have to be aware that we occasionally see very
22 extended incubation periods after heat treatments.
23 And so we kept the mice under observation for up to
24 600 days.
25 The limits of detection depend on

1 concentration of the sample and the toxicity of the
2 sample. We cannot inject material that is toxic,
3 obviously, to the mice. So sometimes dilution factors
4 had to be included so that we could inject the mice
5 and not limit the clearance levels that we can
6 measure. However, we feel that near optimum
7 demonstrate clearance levels are demonstrated from
8 this model.
9 The scaled down to simulate typical
10 gelatin manufacturing conditions was performed by Ad
11 Grobben from earlier and that was reviewed by an
12 international panel prior to initiation, and as
13 already indicated, Ad Grobben is here to answer
14 specific questions on that matter. And the quality of
15 gelatin was checked as the experiments proceeded and
16 again I can address those questions.
17 Next slide. Okay. So this is what was
18 done. The raw materials were 1.5 kilograms of fresh
19 crushed bones and 500 grams of intact calf backbone,
20 spiked with approximately 10 grams of TSE infected
21 grain homogenate. Half this back was injected into
22 the spinal column and the remainder smeared onto bones
23 and dried onto the surface, and the backbone was then
24 sawed into pieces. There was a degreasing process
25 where the bone chips were washing at 85 degrees

1 centigrade to remove soft tissue and fat after the
2 spike had been added, and then dried in the hot air at
3 120 degrees centigrade.
4 Then the demineralization step was
5 performed. The bones were soaked in hydrochloric
6 acids of increasing concentrations. The ossein, of
7 course, remains as already described. Then the liming
8 process, the ossein was exposed to saturated calcium
9 hydroxide of pH 12.5 for the minimum of three weeks,
10 and then neutralized. On the acid treatment left over
11 night, also a pH 3 and then washed in water. The NaOH
12 treatment, which is included in the acid experiment,
13 one acid experiment, the ossein was exposed to .3
14 molars of sodium hydroxide pH 13 for two hours.
15 Then the extraction process ossein was
16 stirred gently with water at temperatures from 60 to
17 90 degrees to a final gelatin concentration of 2.8
18 percent. And then purification steps were performed,
19 depth filtration, ion-exchange, heat sterilization and
20 drying, and all steps were designed to accurately
21 represent the conditions of the industrial process.
22 And it should be pointed out that in the
23 larger process we used indirect heating, but in the
24 industrial skill process, of course, direct steam
25 injection is used.

1 Could I have the next slide? Okay. The
2 spike, as I've already indicated, we use the 301V
3 strain in three of the four experiments, and we use it
4 because it is the most thermostable TSE strain tested
5 so far, and it also is BSE derived. We actually
6 titrated the spike on three separate occasions. We
7 actually had two spikes, Pool 1 and Pool 2, and you
8 can see the values are very similar in all three
9 titrations that we performed with a value of about 7.7
10 in each case.
11 And as I've already mentioned, all
12 clinically negative animals were observed for at least
13 600 days, and then we examined the brains for any
14 evidence of pathological lesions of TSE infection
15 afterwards. And all positive clinical cases were
16 confirmed by pathological examination.
17 Next slide. Okay. Some results. So this
18 is the first experiment where the bone was spiked with
19 301V. The steps were performed degreasing,
20 demineralization and DCP, the dicalcium phosphate,
21 which is a byproduct of the gelatin manufacturing
22 process, was also tested for residual infectivity and
23 we find little. The extract sample after the liming
24 initialization extraction had a little bit of
25 infectivity here, and you can see the individual

1 numbers on the left, and that calculates, according to
2 the Carver Method, to titre of less than or equal to
3 101.8 ID50 per mil.
4 I say less than or equal to, because if
5 you use the Carver Method, you have to make it -- and
6 you've got incomplete groups at either end of your
7 dilution series, you have to make assumptions about
8 what happened in that group. So we don't have a 10+1
9 group, but we assume to get the number 1.8 that that
10 value, all the mice would have gone down the 10+1
11 dilution. So the number over here is the total
12 recovery calculated against the 10 gram spike that was
13 used. So we got from total infective load to 108.7 to
14 total recovery of 10.5.
15 Then the sample was taken through the
16 filtration ion-exchange in concentration steps and the
17 sterilization steps, and a sample was then also
18 measured for infectivity, and no infectivity at all
19 was recovered. And in this case, what these data say
20 is that we couldn't detect anything. We don't know
21 what would have happened if we had been able to inject
22 a more concentrated sample again. So again, we can
23 only say this is the limit of the clearance that we
24 have achieved. So the total recovery is less than
25 103.8 starting with the 108.7.

1 Okay, next slide, please. Okay. So this
2 is the second experiment in the alkaline process where
3 we used the other strain, 263K, and I will go through
4 this a bit quicker. The total infective load is 109.
5 We recovered a little infectivity again and the DCP,
6 the dicalcium phosphate, and we also recovered a
7 little bit of infectivity in the extract sample
8 totaling out to a total recovery of less than or equal
9 to 104.3.
10 Next slide. The acid process here we
11 again had a spike which had a total infectivity of
12 108.8 and following the steps of degreasing,
13 demineralization, then the acid treatment and
14 extraction we had a recovery of infectivity of 106.2.
15 In this case, we got a clear end point to the
16 experiment, because the neat fraction, all the animals
17 came down to 10-2, none did, so a nice, neat Carver
18 calculation of 106.2.
19 After the filtration, ionization,
20 concentration, sterilization steps no infectivity was
21 recovered and we can say that is less than or equal to
22 104 logs of infectivity were recovered.
23 Next slide. Okay. Now, this is the
24 variation on the acid treatment where the sodium
25 hydroxide step was included after the acid treatment

1 had been performed. And when this was done, we find
2 that no infectivity at all was recovered in the
3 titration and we can calculate total recovery of less
4 than or equal to the 103.3.
5 Next slide. Okay. Looking at the data
6 across the way, that's the first alkaline process and
7 you can see it went from 8.7 to less than 5 down to
8 3.8 with no positives.
9 Next. Next? Oh, there we go. Thank you.
10 And this is the alkaline process with 263K, and now
11 you can compare the numbers directly with each other.
12 So we start off with slightly higher spiked titre and
13 slightly lower recovery of infectivity at this point
14 on the crude gelatin extract.
15 Next. And next again. And with the two
16 acid process experiments, we start off with the spike
17 of 8.8, 8.7. We recover a little bit more infectivity
18 than in the alkaline process at the crude gelatin
19 extract, but again when we look at the purified
20 material, no infectivity is recovered and we can, as
21 I already said, indicate the clearance values from
22 that part of the process. And you can see now that
23 the acid process with the included NaOH treatment in
24 here resulted in no infectivity being recovered.
25 Next. So this summarizes the data and now

1 I have included on the right hand side the clearance
2 factors that have been obtained from the experiment.
3 So we can say that the alkaline process, the crude
4 gelatin extracts have a clearance of greater than 3.7,
5 logs of infectivity and for the 263K experiment it was
6 greater than or equal to 4.7. The finishing, the
7 purification and sterilization steps have additional
8 clearance factors that we have demonstrated of greater
9 than 1.2 and that totals over the two parts of the
10 process to greater than or equal to 4.9.
11 In the acid process, we got a clearance
12 from the -- in the crude gelatin extract of 2.6. The
13 sterilized gelatin after finishing has got an
14 additional demonstrated clearance of greater than 2.2
15 and adding that together, we've demonstrated a
16 clearance for greater than or equal to 4.8. And then
17 in the acid process with the additional NaOH
18 treatment, the overall clearance demonstrated is a
19 value of greater than or equal to 5.4 logs of
20 infectivity.
21 Next. Okay. So that summarizes what we
22 have. From the acid bone process, we have got
23 substantial infectivity measured before purification
24 in the third experiment, but complete appearance after
25 -- complete clearance after purification, including

1 sterilization. Complete clearance, no infectivity
2 detected before purification if an additional sodium
3 hydroxide step is included.
4 With the alkaline process, there is
5 greater removal of infectivity than after equivalent
6 acid hydrolysis procedure and there was complete
7 clearance. No infectivity detected after
8 purification, including sterilization.
9 Next. So our conclusions are that the
10 gelatin manufacturing procedure was successfully
11 scaled down and normal bone gelatin was produced.
12 Both degreasing and the standard acid and alkaline
13 treatments alone remove most, but not all, of the
14 implied infectivity before final purification of
15 gelatin. The liming or alkaline procedure was more
16 effective and the additional sodium hydroxide step in
17 the acid procedure inactivates a residual detectable
18 infectivity before purification. After purification,
19 all samples do not show any detectable infectivity.
20 And again, this was pointing out the removal of
21 infectivity is cumulative, but not necessarily
22 additive.
23 Okay. I want to move on to report the
24 data obtained by the Dutch experiment where they
25 applied pressure treatment to produce their gelatin.

1 They started off with titre of their spike, total
2 titre of 9.2. They went through the standard
3 procedures of degreasing and preheating, then did the
4 pressure treatment at 3 bar, 20 minutes, 130 degrees
5 centigrade, then extracted the gelatin. In the crude
6 gelatin extract, they showed that no infectivity could
7 be recovered, and the volume that comes to is less
8 than or equal to 0.2.
9 So they record a clearance factor of
10 greater than or equal to 6.8 with this process. They
11 did nothing -- well, they didn't follow this, the
12 purification steps. They didn't test that, but there
13 was no infectivity in the gelatin solution that would
14 have come through this procedure anyway, so it would
15 have been a waste of time.
16 Next. So risk reduction and gelatin.
17 We've had several descriptions of this already in the
18 earlier session about sourcing using only animals
19 passed fit for human consumption, omission of head
20 bones and vertebrae from source material in BSE
21 infected countries, and we have shown the removal or
22 inactivation steps or removal of TSE infectivity
23 during the gelatin extraction and purification
24 process.
25 It's also worth noting that the species

1 barrier would reduce the effect of titre or BSE being
2 -- if humans were exposed to BSE from the source. It
3 is worth also noting that the acids were performed by
4 injection intracerebrally, and this is by far the most
5 efficient route of infection, other routes of
6 infection are less efficient.
7 Next. I'll skip that. That's it. Okay.
8 Thank you very much.
9 CHAIR PRIOLA: Are there any questions for
10 Dr. Somerville? Dr. Bailar?
11 BOARD MEMBER BAILAR: I have a couple of
12 related questions. First, I find the time
13 deactivation curves somewhat troubling. They suggest
14 that some of the infected agent is being protected
15 somehow. What is your take on that?
16 MR. SOMERVILLE: Exactly that. That there
17 is -- I didn't want to get too much into the
18 fundamental thoughts that I'm having at the moment
19 about that, but I think we're getting a dissociation
20 reaction and a protective reaction occurring when
21 inactivation, heat inactivation is attempted. And the
22 protected species that is formed or the stabilized
23 species is much more difficult to inactivate. It may
24 be similar to the dried material that I was showing in
25 some of the earlier slides, too, and that we know is

1 much more difficult to inactivate.
2 BOARD MEMBER BAILAR: Well, there are at
3 least a couple of other possible explanations.
4 MR. SOMERVILLE: Sure.
5 BOARD MEMBER BAILAR: One is that some of
6 the agents being protected inside little particles.
7 There many be subtle differences in the chemical
8 structure of the ones that survive versus those that
9 don't. Which leads me to my second question. In the
10 intact animal, the infection occurs while the animal
11 is alive. It gets circulated and I would presume gets
12 distributed throughout all the tissues and whatever
13 titre is appropriate for that. In the experiment, the
14 infective agent was added to the bone chips, that is
15 at a considerably later stage of things, where it
16 might be more on the surface of any particles that
17 remain or it might stay on particles and so forth. So
18 I'm asking if you have looked into this, and if there
19 is any reason for concern about this difference in the
20 sequence of when the infection is added to the
21 materials that you are processing.
22 MR. SOMERVILLE: Well, let me answer this,
23 your question this way. I don't know if it actually
24 addresses what you are saying. But the reason for
25 doing the experiment the way we did it was to try and

1 maximize the exposure in the experiment. So the
2 thinking was that the greatest risk of BSE
3 contaminating bones was that during the slaughter
4 process, and that spinal cord, for example, would get
5 spread down the vertebrae column included with it and
6 dry onto it. So that was what was attempted to be
7 mimicked in the experiment.
8 I'm not -- I suppose the other side of the
9 question is how much infectivity in living animals
10 associated with bone and bone related tissue? Our
11 primary concerns in that respect again is to do with
12 spinal cord in BSE infected cattle with spinal cord
13 and ganglia and related nerves and, of course, the
14 brain in the skull. These should be removed, and
15 again we're asking the question what happens if they
16 don't, and we've tried to include that kind of thought
17 in the design of the spiking of the experiment.
18 BOARD MEMBER BAILAR: Have you tried to
19 grow out the infective agent that survives the steps
20 for 20, 40, 60 minutes to see if it remains highly
21 resistent?
22 DR. SOMERVILLE: No, not formally. It's
23 an experiment I want to do, obviously, but I haven't
24 formed it. I don't think -- David Taylor whether he
25 has actually done that experiment, either. My

1 prediction is that it would not be in the protected
2 form after passage through an animal, but we have to
3 do the experiment. Thank you.
4 CHAIR PRIOLA: Dr. Petteway?
5 DR. PETTEWAY: Thanks. I just have a
6 couple of questions about the process of doing the
7 studies and setting them up. Just to make sure I
8 understand, these were scaled down, coupled steps, so
9 that the spike was at the initial step and then
10 removal was monitored throughout the process without
11 respiking it each additional step, correct?
12 DR. SOMERVILLE: That's right. Yes,
13 that's correct.
14 DR. PETTEWAY: Okay.
15 DR. SOMERVILLE: I think the experiments
16 that Dr. Rohwer will describe are looking at process
17 of the final steps in the process with spiking at the
18 beginning of those individual steps.
19 DR. PETTEWAY: Exactly. So that your
20 final removal shows the cumulative effect of the
21 process to remove the input spike.
22 DR. SOMERVILLE: Yes, yes.
23 DR. PETTEWAY: I have one other question
24 and that's with the magnitude of the clearance
25 numbers.

1 DR. SOMERVILLE: Yes.
2 DR. PETTEWAY: And the less than or equal
3 to or greater than or equal to. The magnitude
4 reflects the limit of detection of the assay.
5 DR. SOMERVILLE: Precisely.
6 DR. PETTEWAY: As opposed to what may
7 actually be the magnitude of removal. The magnitude
8 of removal is likely to be much greater than the
9 numbers reflect, because of the limit of detection of
10 the assay, right?
11 DR. SOMERVILLE: Basically, yes. We can
12 only report what we observe.
13 DR. PETTEWAY: Right.
14 DR. SOMERVILLE: But we can also make some
15 predictions about what we know from other parts of the
16 process.
17 DR. PETTEWAY: Right.
18 DR. SOMERVILLE: And that is why, as
19 you've said it before, it's important not only to look
20 at the overall process, but to look at individual
21 steps and evaluate what they may be contributing to
22 the inactivation process or removal process. However,
23 as the study illustrated, for example, we also have to
24 be aware that individual steps will not be additive
25 and that one part of the process may remove the same

1 thing as a later part, later stage might also remove,
2 so you have to be very careful when you're doing that.
3 DR. PETTEWAY: But we can be confident in
4 the linking of these studies that based on the input
5 spike that there was no detectable infectivity based
6 on the limited detection of the assay at the end of
7 the process?
8 DR. SOMERVILLE: Yes, yes.
9 DR. PETTEWAY: And then the last question
10 I have is the additional step with the sodium
11 hydroxide. That was evaluated independently?
12 DR. SOMERVILLE: What? It was a separate
13 experiment, if that's what you mean.
14 DR. PETTEWAY: Yes, that was a separate
15 experiment?
16 DR. SOMERVILLE: Yes.
17 DR. PETTEWAY: Evaluated independently.
18 Okay.
19 DR. SOMERVILLE: Right.
20 DR. PETTEWAY: Thanks.
21 CHAIR PRIOLA: Dr. Hogan?
22 BOARD MEMBER HOGAN: Very nice studies,
23 Bob. I had a question on when you are calculating the
24 clearance factor here, you've listed an equation that
25 says clearance factor is equal to gram spike times 10

1 the log titre spike divided by milliliters of gelatin
2 times correct factor times 10 to the log titre
3 reduction or gelatin. For somebody that can't balance
4 their checkbook, what do you mean by correction factor
5 in the denominator and why was that entered?
6 DR. SOMERVILLE: Okay. The correction
7 factors are to account for the inherent losses in the
8 process by taking a sample out for intermediate
9 titration or other evaluations. So there is natural
10 loss in the amounts going through the process. Does
11 that deal with that?
12 BOARD MEMBER HOGAN: Yes, that's great and
13 it makes good sense. The second question is did you
14 look at any place in the process where titre might
15 have accumulated or concentrated, such as inner
16 vessels or on any of the columns or anything like
17 that?
18 DR. SOMERVILLE: I think the short answer
19 is no. Unless Dr. Grobben would like to comment on
20 that. But as far as I'm aware, there was no specific
21 attempt to evaluate that.
22 MR. GROBBEN: I do want to. I would like
23 to comment to that, I think. No attempt was done to
24 try to measure the infectivity which remains in the
25 equipment, especially for filtration and ion-exchange,

1 because of the problem to extract that infectivity
2 from that equipment, so that was not done. We just
3 measured what was left in the gelatin.
4 CHAIR PRIOLA: Go ahead.
5 BOARD MEMBER HOGAN: That's what I
6 presumed. It's just very difficult to get that stuff
7 off to measure it regardless. Now, am I to understand
8 that in the gelatin processing process that these
9 filters would be reused batch after batch or are new
10 filters introduced in the manufacturing process either
11 in Europe or the United States?
12 MR. SCHRIEBER: May I answer this. There
13 is no reuse. It's a one time use. It may be the
14 answer as well as with the ion-exchange columns. They
15 are regenerated with either alkaline or assay to
16 purify for the next round of ion-exchange. So there
17 is a constant chemical treatment after the gelatin has
18 passed those columns.
19 CHAIR PRIOLA: Okay. If there are no
20 further questions, we'll move on. Thank you very
21 much, Dr. Somerville, and Dr. Rohwer is going to
22 present some data.
23 DR. ROHWER: Can we go to the next slide,
24 the first slide here or do I control it? Are you
25 controlling it or am I? Where is it here? Oh. Yes,

1 please, go to the first slide. Thanks. The gelatin
2 manufacturing process is a diverse one. It has many
3 generic features like the contractionation for plasma,
4 at least I see it that way having worked in both
5 areas. So they needed a protocol representing as much
6 of their collective production as possible. And the
7 steps that we were asked to validate in our laboratory
8 were on bone gelatin.
9 Next. And we used the process parameters
10 that were selected by GME, their scale down and this
11 took a lot of time setting this up. Ad Grobben
12 deserves a lot of credit for this, as was mentioned.
13 And from our end, our major concern was about hazard
14 control, and we spent quite a bit of time on this as
15 well. We did this study at a scale that was much
16 larger than we typically use in the laboratory. We
17 were using meters and liters instead of 100 mls at a
18 time and some of these steps did not fit easily into
19 the valid safety cabinets and that type of thing, so
20 we had to figure out other ways to do them. But in
21 the end, we were successful and it worked without a
22 hitch when we finally got down to doing it.
23 Next. The filtrations, the way this was
24 done is we tested several different types of
25 filtrations that are used across the industry and then

1 pulled the filtrates, and that's what was actually
2 titred. I'll show you that in a moment. And getting
3 them all done though it took quite a lot of time,
4 because of the scale and the precautions we had to
5 take to do it safely.
6 Also, all of the work that is done with
7 gelatin has this complication that it is only liquid
8 above 50 degrees centigrade, so you have to keep
9 things warm. You have to keep them warm on a large
10 scale, and so we developed a lot of technologies for
11 doing that, which the tempering beaker turned out to
12 be one of our best tools, but circulating baths and
13 hot pads were also useful.
14 Next. Next, please. About hazard
15 control, we used safety cabinets, bags to cover
16 everything up during the actual processes. All joints
17 between chromatography column unions and filtration
18 things were -- transfers were covered with plastic
19 sleeves in case they leaked, put things in large pots
20 when we could. We poured nothing. Everything was
21 done by pumping from one vessel to another in a safety
22 cabinet.
23 Next. We are also concerned about cross-
24 contamination simply because of the scale that we were
25 doing this on and also because of the sensitivity of

1 the results. And as a consequence, all new dedicated
2 equipment was used for these steps. Everything was
3 disposed -- most things were disposable. The only
4 things that weren't were the stainless steel
5 filtration vessels and a couple of other things which
6 could be autoclaved under sodium hydroxide for reuse.
7 Next. Next, please. We had a question
8 about -- some discussion about the spike earlier, and
9 I think this was a very gratifying experiment for me.
10 We've been trying to figure out whether our spikes are
11 relevant in our plasma studies and that type of thing.
12 But in the case of bone gelatin, the most likely
13 source of infectivity is CNS tissue. And as a
14 consequence, in this particular case, at least we can
15 say that the brain derived spike is probably the most
16 appropriate spike for testing removal from this type
17 of study.
18 And personally, I think this is the
19 relevant tissue and we can use it with confidence.
20 There are issues about whether 263K or the less
21 adapted BSE strain is more relevant. My feeling is
22 that there are advantages to both. Actually,
23 clinically, hamster 263K looks a lot more like BSE
24 than the less adaptive 301V strain. On the other
25 hand, this is a strain that was devised from BSE and

1 so we use that as well. The important thing is when
2 you do two different strains, is what you're looking
3 for is the point of convergence between the two to
4 give you some confidence that the result you are
5 getting are generalized more.
6 Next. The continuous process was done at
7 the Institute for Animal Health, and we are only
8 working on the end stage process right here. Robert
9 has discussed the rest of this. The continuity was
10 maintained by Ad Grobben, who took copious notes, and
11 we also have a lot of further documentation, which
12 I'll share some of that with you in a moment.
13 Next. So here is the process we have been
14 looking at. This is the part that Robert has been
15 describing right here. Well, actually, they carried
16 it through this stage as well, but the only part of
17 this process that we're going to be dealing with is
18 this part right here at the bottom. The so-called
19 purification steps, the filtration, ion-exchange and
20 UHT sterilization, and we're going to look at step
21 wise removals.
22 Actually, we're going to gang these two
23 together in one experiment. We're going to look at
24 them independently as well, and we're going to compare
25 the cumulative versus the serial with the individual

1 testing of these two steps. This was done just
2 individually.
3 Next. Here is the basic layout of these
4 experiments. We have the infectivity spike. It goes
5 into the crude gelatin, which is taken directly from
6 production at the same stage of production. It's
7 passed through the filtration device. And in the
8 filtration experiments, on one arm, we took the
9 filtrates and took it straight through the ion-
10 exchange columns and then titrated it. On another
11 arm, we took it over here and respiked it, figuring
12 that we may have -- hopefully, we had removed
13 something in the filtration.
14 This spike, at the most, would only double
15 the titre that we started out with here by respiking.
16 If we got any kind of removal here, we're just
17 starting over at this point. And then testing the
18 ion-exchange by itself. We wanted to use this so that
19 we had filtrated material to test the ion-exchange
20 process with.
21 Next. The filtration steps, in fact,
22 involved five different protocols with various
23 compositions of cellulose, sources of cellulose and
24 formulations depending on different manufacturing
25 setups across the industry. The filtrates from those

1 were all pooled and then they were titrated by
2 themselves before being passed to the ion-exchange
3 column over here or respiked on this arm and passed
4 through the ion-exchange columns here. The ion-
5 exchange consisted of two columns, the cation exchange
6 followed by an anion exchange, and what we assayed was
7 the eluate from both, the final eluate from both.
8 Next. And then in terms of the UHT
9 sterilization, the ultra high temperature
10 sterilization, we again started with gelatin from
11 production, infected that, spiked that with
12 infectivity and then did the UHT test and titred that.
13 So it's a much simpler pathway.
14 Next. Next, please. Here is a picture of
15 Ad Grobben setting up the filtration experiments.
16 This is the filter apparatus over here. We're
17 transferring, I believe at this step, we're preheating
18 the filter with hot water that has been heated over
19 here, and I'm not sure that's what we're doing there,
20 but that's what this is doing. This is the hot water.
21 It had to be preheated so that it was warm enough to
22 keep the gelatin melted once we put it in there.
23 We've got another bath heating up the gelatin to dry
24 through the filter.
25 Next. Here's the filter being assembled.

1 It's quite a large apparatus, compared to what we're
2 used to, but we were able to do all of this within the
3 hood, though the transfers had to be through this pump
4 on the outside. There's the filter A being added.
5 Next. Here is the filter A being stirred
6 in the filter and then it's drained to form the filter
7 cake in the bottom.
8 Next. Here is the filtration apparatus
9 setup being done. Here is the vent in case, because
10 you have to vent some air out of it in the early
11 stages, and through HEPA filter here. And here is the
12 assembly after the filtration is over.
13 Next. This was a keeper in that
14 experiment, and this was a failure. We always
15 inspected the filter cakes after the filtrations to
16 make sure they were intact. There were no
17 possibilities of leaks and that kind of thing before
18 we would keep the filtration as a successful one. And
19 so the only thing that goes into this study were
20 successful filtrations.
21 Next. Here is a picture of the column
22 apparatus, the ion-exchange apparatus. These were
23 gigantic by our standards. We set them up on a mobile
24 cart on a chromatography rack that we can roll, so
25 that once we got everything setup and ready to go, we

1 could roll the cart over a very large plastic bag and
2 then cover the whole thing in this plastic bag and
3 seal it up during the actual experiment in case there
4 were leaks. Thank God there were none.
5 Next. And here is the apparatus that we
6 used for the UHT Inactivation Experiment, and I can
7 make that a little clearer in the next slide, which is
8 diagrammatic.
9 Next. The principles that we are trying
10 to employ in the UHT study that we were trying to
11 mimic from the actual production environment is, from
12 my prospective in studies that I'll talk about later
13 this afternoon, infectivity is not intrinsically
14 resistent. The problem is delivery of the inactivant
15 and the inactivant finding sanctuaries to hide from
16 the steam, and drying is -- drying into a film is one
17 of the biggest problems.
18 And one of the nice features of the UHT
19 process is the gelatin is being pumped through a pipe
20 in which live steam is being injected. There is no
21 head space. There are no sanctuaries. There is no
22 place for this stuff to dry. There is no place for it
23 to escape from the hydrolytic environment. We wanted
24 to duplicate that as best as we could.
25 Next. Next, please. So we did that with

1 this apparatus where we filled this stainless steel
2 capillary and we used this capillary so that we could
3 affect a very rapid heating and cooling, because the
4 whole process, the UHT process, is a 4 second exposure
5 to 140 degrees centigrade. So how do you do that in
6 4 seconds? Well, you have to get the heat to it in a
7 hurry. We didn't try to do it dynamically. We did it
8 statically. But we did it in this way.
9 So we have this chromatography capillary
10 here. We have a thermocouple, which is embedded in
11 the tube. The probe is right about here. We have
12 another thermocouple on the outside to track what is
13 happening in the bath. And then to relieve any over
14 pressure in the device, we have a water column going
15 here to a back pressure gauge, which ultimately if it
16 were to leak, it would go into this tube right here.
17 And this relieves the hydrostatic pressure that is
18 developed by the fact that we're heating this gelatin
19 up in here. But we've got within the gelatin column
20 itself, we have no head space.
21 Next. We'll take that and the way we get
22 our rapid heating is through trial and error. We set
23 up a protocol where we can dip this thing, hooked to
24 its various thermocouples, up to this recording device
25 into our 160 degree oil bath and then as we see the

1 temperature hit our target transfer temperature, which
2 was about 80 degrees, we quickly dump it into the 140
3 degree bath and it comes to equilibrium in the
4 successive period. We then take it from there after
5 4 seconds has elapsed and dump it into the other
6 temperature. We're tracking this whole thing on the
7 computer. We're watching it in real time as we're
8 doing it.
9 Next. So we get curves like this. This
10 is seconds down here. This is degrees over here.
11 This is the outside of the capillary tube. So we're
12 seeing the capillary dipped into the 160 degree bath,
13 and here we're seeing the transfer into the 140 degree
14 bath, and we're seeing it come to -- and this is the
15 internal thermocouple and it is coming to temperature
16 very quickly thereafter, and then at 4 seconds we
17 plunge it into the water bath and that's the way
18 there.
19 Now, what I showed you first was the
20 hamster experiment. We have now advanced to the mouse
21 experiment. And there is one important difference.
22 As we got more and more experienced with this, we were
23 able to get this ramp time down to shorter and shorter
24 periods. We had about 4 seconds on the first one and
25 about 1 second here. We did four or five trials,

1 actually, three in the end we focused on once we got
2 the method working. And then we picked the best of
3 those trials. And what I have shown you is the
4 temperature records for the two best trials for mouse
5 and hamster and that's what got titrated.
6 Next. Next, please. This is the results
7 of all these experiments. The pooled filtrates gave
8 a very disappointing clearance. I was expecting much
9 higher than that. The respiked column gave this, only
10 about a half log removal, and remember for these types
11 of input titrations, we got about a .3 log error
12 associated with these numbers. The successive
13 filtration and ion-exchange gave about 1.8, which very
14 interestingly, but probably somewhat randomly, is
15 exactly the same as the added values between these
16 two.
17 But I think it gives us some confidence
18 that putting these things together, even though the
19 removal at each step is low, we are getting some
20 significant removal here of about 1.5 to 2 logs. The
21 UHT sterilization by comparison gave a much better
22 result. Even that 4 second exposure is giving us
23 about 4 logs of removal. Attached to this, we have
24 about 6 logs cumulative. And I think it is legitimate
25 to attach these, because these are quite different

1 methods of removal versus inactivation.
2 Next. And this is just a comment on that,
3 these things were showing independent removal to the
4 extent that we could detect it with the lower levels
5 that we saw there. But in terms of looking at the
6 total, at what was actually going on there, the serial
7 experiment is actually the best one to use, and that's
8 the one I think we should focus on. But both of these
9 steps were much less effective than I had expected.
10 And I don't know whether it is because of the matrix,
11 the apparatus, the gelatin itself, but in the next
12 slide I'll show you some data.
13 Next, please. In our experience, this is
14 about half these experiments were done by us. The
15 other half were done by other folks, but they were
16 compiled for a former presentation of the FDA and a
17 TSE Advisory Committee meeting in October 7, 1997.
18 And typically, and we've done more of these since
19 then, especially these depth filtrations, and they are
20 typically removing 3 logs or better.
21 So there's something different about
22 gelatin. And it's either the way we did the
23 experiment or it could be that the gelatin is so
24 overwhelming in terms of a competitive binder for the
25 matrix that we're not getting removal because of that.

1 But anyway, it doesn't fall into expectation. There
2 is a warning in this though, which says that you have
3 to check these things. You can't extrapolate from
4 this cumulative experience and presume that it's going
5 to work in all cases.
6 Next. I've already dealt with this.
7 Let's go on. Next, please. I just want to point out
8 that this UHT result is the worst case result. We did
9 it under static conditions. It is heated from the
10 outside instead of the inside. 4 seconds is a minimum
11 exposure that is seen in the industry. And we're
12 using crude brain homogenate instead of material that
13 has been already refined by the process. And my guess
14 is that the stuff that has been through the process
15 may be even more susceptible, but that's a guess.
16 Next. I want to make one final point and
17 that is that the total exposure that these samples got
18 really begins, at least for sure, with the 263K case,
19 with the 80 degree exposure. I mean, somewhere
20 between 80 and 100 degrees. We have a series of
21 experiments which are actually on the next slide that
22 I did in the '80s showing that we start to see affect
23 around 100 degrees, and we get total killing in a few
24 seconds at 121.
25 So this ramp temperature is also

1 contributing to the inactivation here. And if we take
2 these ramp temperatures and add it from 100, the ramp
3 exposure plus the exposure temperature for the 263K
4 case and the 301V case and plot them on the same
5 curve, which I'm going to do next.
6 Next, please. This is just showing you
7 that there is an effect at 100 degrees and above for
8 the 263K case, at least.
9 Next. These are the ramp times for those
10 former experiments.
11 Next. Let's go on. Next. I just want to
12 show you this last slide. If you plot the data from
13 the 301V case and the 263K case on the same time axis
14 down here, including these earlier studies out here
15 which were done at 121 versus 140, and plot it back to
16 the origin, you get a straight line through these
17 things. Well, I first draw the line through them.
18 And what that is telling me is two things.
19 One, there isn't really any significant
20 difference between the sensitivity of these two agents
21 to this process. And two, it gives me some confidence
22 in saying that if you are to extend this process to 10
23 or 12 minutes, you get another 4 logs or so removal.
24 This is something that should be checked with actual
25 kinetic experiment and kinetic measurements, but it

1 seems to me that this being a minimum is a very --
2 this 4 seconds being a minimum exposure is a very
3 encouraging feature of this experiment.
4 Next. In conclusion, the purification
5 steps are removing 4 to 6 logs and the UHT step, in
6 particular, provides a potentially very secure
7 inactivation step. Thank you.
8 CHAIR PRIOLA: Dr. Bailar?
9 BOARD MEMBER BAILAR: The next to the last
10 slide you showed the susceptibility to heat over time,
11 and what you had you mentioned the straight line fit,
12 but I didn't see any intermediate points there that
13 could really detect curvature in the line.
14 DR. ROHWER: No, there isn't. What I'm
15 saying is we're working with the data that I have.
16 And I think I also said at the same time that it would
17 be very nice to do a complete kinetic study on this.
18 BOARD MEMBER BAILAR: Yes, but I would not
19 conclude from that that it's a straight line.
20 DR. ROHWER: Oh, I see what you're saying.
21 It may not be. You're right. From here to here,
22 well, from here to here, extrapolation, I don't know.
23 I mean, it's hard. I guess, what would you say? You
24 could have something like that, I guess.
25 BOARD MEMBER BAILAR: I would say you do

1 not have the evidence on which to detect whether there
2 is any curvature.
3 DR. ROHWER: Okay. Well, I'll grant you
4 that. And all I'm saying is that this is -- let's put
5 it this way, this data is consistent with a first
6 order process here, with these two samples behaving
7 very, very similarly.
8 BOARD MEMBER BAILAR: Okay. That's all.
9 CHAIR PRIOLA: Dr. Petteway?
10 DR. PETTEWAY: That's a very impressive
11 set of experiments, Bob, especially dealing with the
12 scale down, handling it all. That's an extremely
13 difficult thing to do. But the 4.2 logs, was that the
14 magnitude with some residual infectivity found?
15 DR. ROHWER: Oh, yes.
16 DR. PETTEWAY: Okay.
17 DR. ROHWER: Yes, I mean, we started with
18 7.5 logs.
19 DR. PETTEWAY: Yes.
20 DR. ROHWER: So there's still 3 or 4 logs
21 left.
22 DR. PETTEWAY: And that was at 4 seconds
23 which is worst case?
24 DR. ROHWER: Yes.
25 DR. PETTEWAY: And what you're saying, I

1 mean, even given other points that would show a change
2 in that curve, the likelihood is 8, 10, 12 seconds,
3 there would be nothing left is the point?
4 DR. ROHWER: I was very interested this
5 morning when Michael Dunn pointed out in his
6 presentation that in North America anyway the typical
7 time is 8 to 16 seconds, as opposed to 4 seconds, and
8 apparently gelatin can tolerate that quite well. If
9 you would like to say something about that? Well,
10 that's up to Sue. Sorry.
11 CHAIR PRIOLA: Dr. Dunn, do you want to
12 comment on that?
13 DR. DUNN: Could you say it again?
14 DR. ROHWER: Yes, if I could repeat that,
15 what I just heard here is that there is apparently no
16 problem extending that time for 8 to 16 seconds.
17 CHAIR PRIOLA: And Dr. Hogan?
18 BOARD MEMBER HOGAN: Well, the question is
19 why does the European process use 4 seconds and is
20 there a ramp up time to that or is it just the batch
21 is brought in, zap 4 seconds and then it is taken out?
22 DR. ROHWER: I would like to defer to Mr.
23 Schrieber, if I could.
24 CHAIR PRIOLA: Yes, Mr. Schrieber?
25 MR. SCHRIEBER: What I explained in my

1 presentation already is that we used the softest
2 condition we have found in one of the gelatin plants
3 in Europe. So it's not uncommon to have like in the
4 States a longer temperature or even a somewhat higher,
5 longer time or even somewhat higher temperature, but
6 we had to choose the minimum conditions founded in the
7 three or four studies, and that's what it is. You are
8 right if the time would be expanded to 6 seconds or
9 the temperature would go up to 140 instead of 138,
10 this would not really harm the quality of the gelatin.
11 CHAIR PRIOLA: All right. If there are no
12 other questions, thank you very much, Bob.
13 (Applause)
14 CHAIR PRIOLA: I would just like to say
15 having gone through the bulk of this, these
16 infectivity studies in our rather thick handout, that
17 it is very impressive the work that Drs. Taylor,
18 Somerville, Rohwer, Ad Grobben and Schrieber have done
19 studying inactivation of TSE infectivity through the
20 gelatin processes. It's a lot of real nice work.
21 I would like now to ask Dr. Morris to come
22 up and explain to us the USDA's gelatin policy.
23 DR. MORRIS: Okay. Good morning and thank
24 you for the opportunity to speak with your Committee
25 regarding APHIS's policies regarding the importation

1 of gelatin.
2 COURT REPORTER: Dr. Morris, hit the
3 volume button.
4 DR. MORRIS: Thank you.
5 CHAIR PRIOLA: I'm sorry. My apologies.
6 It was supposed to be Dr. Rogers. I'm very sorry.
7 That's my error. Can we just go with that?
8 DR. ROGERS: Yes.
9 CHAIR PRIOLA: Okay. My apologies. I'm
10 sorry. You should have told me. I'm misaligned in
11 the agenda. Okay. So, in fact, we're not going to
12 hear from Dr. Morris yet. It's Dr. Rogers who is
13 going to give us a risk analysis of infectivity.
14 DR. ROGERS: Well, I guess the slide has
15 disappeared for a minute there, so don't start the
16 thing until -- the timer until it shows up. Is the
17 mike on? Okay. Thanks for inviting us down here
18 today from Canada. I'm from Health Canada.
19 CHAIR PRIOLA: We can't hear.
20 DR. ROGERS: So is the mike on? Oh, it's
21 on now? Oh, closer. Taller and closer. How's that?
22 Okay. At Health Canada we have been doing a number of
23 quantitative risk assessments and part of our topic
24 today that we will be covering is what's on your
25 agenda. But I did want to say that what we're really

1 looking at is the varying-CJD risk to consumers eating
2 foods containing small amounts of processed ruminant
3 products. And I want to talk about some of our
4 modeling functions.
5 Next slide, please. We have just
6 completed a quantitative risk assessment for basically
7 products that contain beef extracts and the beef
8 extract industry certainly has a lot of similarities
9 to the gelatin industry, so some of the information
10 I'm going to provide today will certainly with some
11 understanding of the overall picture. I do want to
12 present today like the quantitative model parameters
13 for the evaluation on pairing CJD risks. I want to
14 focus on the front end parameters for risk analysis,
15 and I want to provide some information on evaluating
16 uncertainty in the parameters and provide information
17 on variability that we're using in our models.
18 Next slide, please. The purpose of our
19 risk assessments are really to provide information on
20 two risk outcomes of the probability of individuals
21 acquiring varying-CJD through the consumption of a
22 product and the annual number of varying-CJD
23 infections that could be predicted.
24 Next slide, please. The approach that
25 we're using, basically, the first thing that we look

1 at is the length from BSE agent to varying-CJD. To
2 date, there is no direct evidence linking the
3 acquiring of varying-CJD to particular products. And
4 I want to emphasize that certainly the only
5 information we had previously was the work of Simon
6 Cozens of the UK for food products which had some
7 implicated meat pies, sausages, these types of things
8 in his work, but he has, in fact, recalculated his and
9 reevaluated some of that publications and in Edinburgh
10 last year he has, in fact, shown there has been no
11 statistical significance to particular food products
12 and varying-CJD. So that's an important picture.
13 The presence of the BSE agent in the
14 product of concern are not measurable by our current
15 techniques. The only thing that we can actually still
16 seem to have some type of laboratory analysis for is
17 the presence of CNS materials through IHCGFP and some
18 neuro analyst techniques. The hazard identification
19 basically has established that there is a route from
20 BSE to consumption exists. And so that's the reason
21 for the presentation of the modeling.
22 Next, please. In Canada, we are using the
23 model that has basically been setup by the Kodak
24 element. We have an issued statement. We do hazard
25 identification, hazard characterization, exposure

1 assessment and risk characterization, but nothing goes
2 forward until you have hazard identification.
3 Next slide, please. Our structure in our
4 risk characterization is depicted here. Basically, we
5 are looking for these probability statements in the
6 middle, which are outcomes, but we are looking at the
7 infectivity consumed, which really comes through our
8 exposure assessments and the consumption frequencies
9 from the exposure assessment, and then the dose
10 response models that we have been developing, which
11 are in the hazard characterization.
12 Next slide, please. Our structure in
13 hazard characterization, basically, the main things,
14 variables that we would be looking at are the
15 susceptibility in human population. We can say that
16 certainly the we in our risk assessment are looking at
17 worst case assumptions. In fact, with the human
18 population, we are not looking at divergence, for
19 instance, because of met type of codons, we say that
20 all humans are susceptible. We're not looking at
21 immuno-compromised or younger children. There's no
22 infant instances of that, so like our population
23 characteristics say that all populations are
24 susceptible.
25 Infectivity accumulation is one of the

1 things we are looking at particularly with dose
2 response type of modeling. Our species barrier from
3 bovines to humans, I guess, what I would say there
4 again is that we are looking at the worst case. We're
5 saying that there is no species barriers. It's a 1 to
6 1 ratio, but certainly when we're looking at the
7 advice that we get from the Scientific Steering
8 Committee over in Europe that they say that we should
9 use the range of 1 to 10,000.
10 And, in fact, the latest publications do
11 say for oral transmission to food products, you
12 probably should be looking at 10,000. And we are
13 looking at risk assessments to be tried and say, for
14 instance, they do want things to be practical and
15 realistic, but then we are going with due caution.
16 And so some of these products that we're looking at to
17 start with, we are emphasizing generally worst case
18 assumptions and seeing what those numbers generated
19 look like, and so that's what we have been doing.
20 Next slide, please. In particular, it's
21 the dose response area for varying-CJD. And in our
22 models we are using a threshold dose response as well
23 as an accumulation dose response. I have a lot of
24 slides here, so I'll have to hurry along with this.
25 We'll talk about that a little further along.

1 Next slide, please. The structure and our
2 exposure assessment just basically analyze the model
3 that we use.
4 Next slide, please. And particularly,
5 which is of interest to this particular audience is
6 the fact that we are looking for the presence of BSE
7 in cattle populations. Our models are setup in such
8 a way that we do know that the disease status of a
9 country changes and I think we have that from our own
10 experience, but we have them working along the lines,
11 for instance, that food products and gelatin products
12 are produced over periods of time, so the BSE status
13 and the amount of BSE possibly infected cattle in the
14 country change, and so we really want to be able to
15 adapt that to the different lots and processes.
16 The tissue infectivity information that we
17 use, basically, a lot of it from the oral pathogenesis
18 studies to start with from Dr. Wells group and that
19 continues on in the UK. Our source of infectivity in
20 the slaughtering areas, our sources of infectivity
21 certainly depend on the tissues that are used in the
22 products, and I think you've been discussing a lot of
23 those today with specified risk materials, for
24 instance.
25 And this area here I put the word gelatin

1 for the commercial product of what we're looking at.
2 In fact, this model was developed particularly for
3 beef extracts, but it is the front end that I wanted
4 to talk about today. Because what we've been doing as
5 well as we do look at consumption, the actual final
6 products, the amount of material that are in final
7 products, and then the amount that go to consumers and
8 consumer individual servings.
9 Next slide, please. So our quantitative
10 model prevalence of BSE into -- the BSE infected
11 bovines in populations in the screening procedures.
12 The inference from the countries of BSE surveillance,
13 first of all, I want to say one thing and that is that
14 the products we were looking at were generally ones
15 that were coming from the European Union or could have
16 been coming from other places. But when we were
17 looking at prevalence data itself, because of the wide
18 enhanced surveillance targets that have been going on
19 in the EU that we particular have some good
20 observational data there to work backwards from.
21 And I must say that certainly the EU has
22 also been doing a lot of missions out to their member
23 states to go for audit and compliance, and they have
24 been doing a number of good reports on that. That's
25 why we get some excellent data to sort of give some

1 parameters around to put in models. However, I'll
2 tell you that particularly our concerns are detected
3 diagnosed cases are removed from -- are diverted from
4 food chains.
5 But the incubating cattle are a question
6 in the amount of infectivity in incubating cattle,
7 certainly one of the major things that we have been
8 struggling with. But in our particular assessments,
9 we're using 4 incubating cattle per adult cattle
10 diagnosed and we've done that, basically, from talking
11 to experts in Europe. And the other thing that we're
12 doing, though, is that we're talking about the
13 infectivity of tissues.
14 We started off with giving them exactly
15 the same infectivity as the clinical animals to run
16 through the worst case numbers, and then we scaled
17 that backwards. But I'll explain a little bit later.
18 But what we've done is basically we try to group
19 countries into low, medium and high prevalence rates
20 and so then I do have numbers on that, but again this
21 presentation is going to be a little small for that,
22 but we'll get to that.
23 As far as the abattoir screening itself
24 it's concerned that certainly now there are rapid
25 tests involved, and we've seen that they were talking

1 about 100 percent sensitivity, 100 percent
2 specificity. There's a number of rapid tests out
3 there. We have done an evaluation of them and we've
4 used the worst case sensitivity for one particular
5 rapid test, because we cannot tell because there are
6 varied tests that have been used in similar countries
7 and so you don't necessarily have all that
8 information.
9 But for modeling purposes, again, we're
10 using the worst case. And for the ante-mortem,
11 postmortem inspections only for diverting BSE infected
12 cattle from the food chain, we're using a 2.5 percent
13 removal from ante-mortem. And I think most people
14 know how very difficult it is to diagnose TSE diseases
15 and that they are very complicated.
16 However, they have gone back and it is a
17 requirement in the European Union to, in fact, state
18 where you are during your diagnoses, are they ante-
19 mortem or are they rapid test. And so that the range
20 of variability in ante-mortem depends on the country
21 and in the awareness, the education and in a lot of
22 infrastructure elements. However, I can tell you that
23 for what we've done, I've only seen six reports so far
24 from mission compliance audit states and the lowest
25 amount of divergence is 3 percent out of Belgium from

1 ante-mortem and up to in the high 30 percents in
2 Germany. So there's a lot of variability in the
3 amount of BSE infected animals that are removed
4 postmortem. And this goes into the models as well.
5 Next, please. Next, please. Oh, sorry,
6 I couldn't see it right. Okay. So now, I'm looking
7 at tissue infectivity. I just want to give a brief
8 run down here that we are using .1 gram of raw
9 unprocessed brain tissue from a clinically infected
10 bovine as the minimal or as the threshold dose in our
11 models, at this time. I think that most of you are
12 aware that that is the amount of unprocessed tissue
13 now that has been orally given to a cow that has come
14 down with BSE in the UK in the latest pathogenesis
15 studies. That animal was 52 months. Again, like a
16 very low dose, but it is our starting point.
17 However, we do put uncertainty around
18 these things, again, up to, per program, 101 to 103
19 infectious doses. And then the infectivity that we
20 are assumingly using the same infectivity scaling
21 standardization to the trigeminal root ganglia, the
22 dorsal root ganglia, the spinal cord and emboli could
23 possibly go into this slaughtering and stunning
24 procedures. And I have mentioned already we are
25 looking at the incubating bovine, and particularly the

1 sensitivity issue around that, and so we have a scale
2 at different levels in our final results.
3 Next, please. Our sources of infectivity,
4 particularly, when we are looking at raw materials, it
5 could be going into things like gelatin. Our CNS
6 emboli in the blood, possibly spinal column cross-
7 contaminations, blood itself, edible fat
8 contaminations, bone marrow, spinal column, and
9 trigeminal ganglia.
10 Next, please. And, in fact, this is the
11 way that we have started in our beef extract risk
12 assessment that we sort of look at in terms of tissue
13 restrictions and no tissue restrictions, and
14 particularly, although I guess this was the top line
15 here that would be very much parallel to what could,
16 in fact, be going on in the gelatin industry, because
17 in beef extract, we do have some productions that only
18 use muscles only.
19 Next, please. One of the things that we
20 see are really the number of bovines that are, in
21 fact, going into batches and lot production and silo
22 storage in beef extract and this is very similar to
23 some of the things you are seeing in the gelatin
24 production. So that we do have, in fact, calculated
25 the probability of a batch contamination, lot

1 contaminations by the prevalence rates and by -- well,
2 it's a little complicated here for me just to go over
3 that quickly, but it's those calculations that we were
4 looking for to say that there's a probability that the
5 consumer product is made from a contaminated product
6 at that end.
7 And so we are looking at the number of
8 infected bovine tissues that go into the batch or lots
9 based on those country prevalence ratios as well. We
10 also are looking at the infectivity reductions,
11 because in beef extract production, as well, you get
12 a lot of heating, wet heat, filtering, decanting and
13 denaturation and, in fact, we have tried to mix
14 estimations on the log reductions there.
15 Next, please. In terms of defining our
16 concerns and characteristics for these products, and
17 I suppose this is one of the difficulties that we do
18 have with food products that contain small amounts of
19 a ruminant product ingredient, not always on the
20 labels and not always necessarily going to the
21 ingredients. In the beef extract production business,
22 for instance, there is no GME type organization.
23 We, in fact, had to go to every country,
24 major country, around the world that does have beef
25 extract production and do our individual

1 investigations by companies to find out the capacity
2 of their equipment, the number of animals, for
3 instance, that -- first of all, one animal contributes
4 so much tissue per lot, and so there is a range of
5 animals that go into lots or batches. And so the
6 probabilities are all derived from that type of
7 information.
8 And so like that's something I'm --
9 actually, I skipped over that a little bit, but it's
10 very important for this type of estimation of, for
11 instance, that even if you did have a BSE infected cow
12 going to gelatin production, for instance, you have to
13 know the capacities of the equipment and the type of
14 equipment and the different processes and certainly
15 that the gelatin industry have indicated that there
16 basically are very similar processes, a little
17 different in the other areas.
18 I see I'm at stop time already, but I just
19 need to go to the next slide, please. Basically,
20 these were the variabilities and the components that
21 we've been looking at, and I'm probably way over time
22 here. But can I just kind of continue on just real
23 quick? Okay? Because certainly like our particular
24 interests is really in the production methods
25 themselves, the production practices, the sources of

1 infectivity, all of these that we've quite clearly
2 documented in our written reports, which we would be
3 glad to share with this Committee at a later time.
4 And the consumer product characteristics
5 themselves, because there is differences amongst the
6 groups of products and within the groups of products.
7 And so we have gone through actual analysis of the
8 amounts of materials that go in there, and then the
9 consumption characteristics themselves, because each
10 product has a different consumption characteristic and
11 so we've tried to work that through with a point
12 estimate of the maximum values.
13 Next, please. And the uncertainty issues
14 that we really weren't looking at in our reports and
15 reporting them as sensitivity, you really have to do
16 a tissue infectivity incubating bovines or species
17 bearing the dose response.
18 Next, please. And if you want to -- next,
19 please. Because this is basically the charts that we
20 prepare, and we are providing like product groups
21 within our report.
22 Next, please. The BSE prevalence is
23 basically put into our charts.
24 Next. Our abattoir screening techniques.
25 Next. For divergence of BSE animals.

1 Next. Other production methods that we
2 have been going through with all information we
3 collect and we can provide that as a range.
4 Next. And then we've done production
5 parameters which are a range of ranges depending on
6 the type of processing, etcetera, and the types of
7 tissues that are added.
8 Next, please. And I think I'll skip this
9 one right now. Next, please. Next. And this
10 basically is just giving us some information on if
11 you're using rapid test and ante-mortem tests.
12 Next, please. Because it was this type of
13 scatter diagram that we're trying to provide to sort
14 of show or give the information on the probability of
15 the consumer batches themselves. If you've got large
16 batches, small batches, high prevalence, low
17 prevalence, and so we tried to do some diagrammatic
18 information in our reports to give some idea of the
19 dilution of tissues with no infectivity or with
20 infectivity.
21 Next, please. And the difficulties I have
22 talked to, and next, please. Bottom line is that
23 these are the individual outcomes that we have been
24 trying to quantify in our risk assessments, and
25 particularly, though that we -- you will find that you

1 can have a lot of problems with surveys, nutrition
2 surveys, etcetera, for the types of details that you
3 would be looking for for trying to get estimates on
4 consumption values.
5 I'm sorry to have gone over.
6 CHAIR PRIOLA: Okay. Well, thank you.
7 Are there any questions for Dr. Rogers? Yes?
8 BOARD MEMBER WOLFE: You mentioned earlier
9 on that your assumption of the ratio of incubating
10 cows to infectiveness is 4 to 1. What is the basis
11 for that?
12 DR. ROGERS: Excuse me, well, that's
13 basically expert opinion from Europe, because like we
14 had talked to people that had the experience with BSE
15 for a number of years, and so that that is just
16 strictly an expert opinion. There's no rationale for
17 that except there is a range of incubating cattle that
18 we do use, but I can tell you the reason why we're
19 using 4, at this time, is because we have implied such
20 harsh assumptions to the fact that there is, it has
21 the same amount of infectivity as the clinical animal.
22 BOARD MEMBER WOLFE: Can you tell me what
23 the range is that you said that you use it for? What
24 is the range or ratio?
25 DR. ROGERS: 4 to 10.

1 BOARD MEMBER WOLFE: 4 to 10. Thank you.
2 CHAIR PRIOLA: Okay. Thank you again, Dr.
3 Rogers. After carefully checking my agenda, now,
4 we're going to hear from Dr. Morris from the USDA. I
5 apologize again for putting you on the spot earlier.
6 DR. MORRIS: Good morning. Thank you
7 again for the opportunity to share our Agency's policy
8 on gelatin. Next slide, please.
9 I am Dr. Terry Morris with the National
10 Center for Import/Export. I am representing the
11 United States Department of Agriculture, Animal
12 Implant Health Inspection Service, Veterinary
13 Services.
14 Next slide, please. We are headquartered
15 out of Riverdale, Maryland.
16 Next slide. And we are under the
17 direction of Dr. Karen James-Preston.
18 Next slide, please. Title 9, Code of
19 Federal Regulations, Part 94, 95, 121 and 122 gives
20 APHIS the authority to regulate animal products. Part
21 94 gives us the authority to regulate gelatin.
22 Next slide, please. We regulate gelatin
23 based on the presence or absence of BSE and the
24 association with the BSE affected region, BSE being
25 Bovine Spongiform Encephalopathy. We have lumped

1 gelatin into one of three categories. One category
2 would be gelatin that is derived from non-ruminant
3 species. A second category would include ruminant
4 gelatin that is derived from cattle that have no
5 association with a BSE affected region. And the third
6 category is ruminant gelatin that has been derived and
7 has an association with a BSE affected region. For
8 the gelatin that has an association with a BSE
9 affected region, those regulations are found in Part
10 94, Section 18(c).
11 Next slide, please. And pretty much to
12 summarize, 94.18(c), the gelatin that is derived from
13 ruminants and the ruminants are from a BSE affected
14 region, that gelatin is prohibited entry, unless the
15 gelatin is imported for human food purposes,
16 pharmaceutical products, photography or any other
17 similar uses that would not result in the gelatin
18 coming in contact with ruminants in the United States.
19 Next slide, please. 94.19 addresses
20 gelatin derived from non-ruminant species. This would
21 include your pig, horse, poultry and fish gelatin. On
22 May 27, 2003, an interim rule was signed that modified
23 the current verbiage in 94.19.
24 Currently, next slide, please, the gelatin
25 that is imported that is derived from pigs, horses,

1 birds and fish species must be accompanied by an
2 original official certificate endorsed by the full-
3 time salaried veterinarian responsible for animal
4 health of the exporting country, and it must state the
5 animal species of origin.
6 Next slide, please. 94.19 also deals with
7 gelatin derived from ruminants, provided those
8 ruminants have not been in a BSE affected region.
9 Next slide, please. This part of the
10 regulation requires that each shipment should be
11 accompanied by an official original certificate
12 endorsed by the full-time salaried veterinarian
13 responsible for animal health of the exporting
14 government, and that certificate must state four
15 things. The first thing it must state the animal
16 species from which the material is derived. The
17 second statement must include the region in which the
18 facility where the material was processed is located.
19 The third statement would include a statement that the
20 material was derived only from ruminants that have
21 never been in a BSE affected region. And the fourth
22 statement must address dedicated facility conditions,
23 meaning the facility cannot receive, store or process
24 any ruminant material from any BSE affected region.
25 Next slide, please. The last category

1 deals with ruminant gelatin that has been associated
2 with a BSE affected region.
3 Next slide, please. Ruminant gelatin that
4 has been associated with a BSE affected region must be
5 accompanied by a veterinarian import permit. A permit
6 is a legal document that authorizes the importation of
7 controlled materials or organisms or vectors into the
8 United States. For ruminant gelatin associated with
9 a BSE affected region, the permit would address the
10 country of origin. It would address the animal tissue
11 species, meaning hide or bone. It would address the
12 exporting and the processing country of origin.
13 Again, we're looking at BSE-free versus BSE affected.
14 Next slide, please. The next few slides
15 depict scenarios that address how APHIS would regulate
16 the importation of ruminant material under certain
17 circumstances. In this scenario, the ruminant
18 material whether it be hide or bone is derived of
19 ruminants from a BSE-free country, but it is processed
20 and exported in a BSE affected country. In this case,
21 we would issue a permit for this material.
22 The permit would require that the
23 government certify the country of origin of the raw
24 animal materials and the government would also have to
25 certify specific conditions that exist within that

1 facility and the BSE affected region. Again, that
2 facility would have to be a dedicated facility,
3 meaning it cannot store, receive or process any
4 ruminant material from any BSE affected region, with
5 the exception of milk and hides.
6 Next slide, please. In the second
7 scenario, we address high derived gelatin only,
8 sourced from ruminants. In this case, whether the
9 hide is derived from ruminants from a BSE-free or a
10 BSE affected region, the fact that it is processed in
11 a BSE affected region requires the need for the
12 permit. The permit, when issued, would require that
13 the government certify that the gelatin is hide
14 derived only, and again because the facility is in a
15 BSE affected region, the facility would have to be
16 dedicated.
17 Next slide, please. The last scenario
18 addresses bone derived gelatin. For bone derived
19 gelatin, and in this case, the ruminants are from a
20 BSE affected region. This material is allowed entry,
21 provided the individual obtains a permit. And when we
22 issue the permit, the permit would require that the
23 individual maintain affidavits that they obtained from
24 individuals who they distribute this gelatin to. The
25 affidavits would require that the individual certifies

1 that the material will not be used as livestock feed
2 ingredient.
3 The material cannot be incorporated into
4 veterinary pharmaceutical uses or the material cannot
5 be incorporated into veterinary biologic products.
6 And this goes back to 94.18(c), which says that the
7 material can be imported, provided it is imported for
8 human food, pharmaceutical products and other uses,
9 photography, and other uses that does not result in
10 the material being introduced to U.S. ruminants.
11 Next slide, please. To complete the
12 process for obtaining an import permit, you have to
13 submit an application, which is VS form 16-3. It
14 takes about 2 to 3 weeks between the time that we can
15 process the application and turn around a permit to
16 you. The application can be submitted electronically
17 through our website. It can be submitted by fax or my
18 mailing it into our office. The permit is good for
19 one year, and the permit will only allow for the
20 specific commodity requested from the specific
21 exporters, and it would have to go to the importer
22 that requested the permit.
23 Next slide, please. This is my contact
24 information, in the event that you need to contact our
25 office.

1 Next slide, please. And again, I wanted
2 to thank the Committee for the opportunity to share
3 APHIS policies regarding the importation of gelatin.
4 I'm happy to answer any questions you may have.
5 CHAIR PRIOLA: Dr. Wolfe?
6 BOARD MEMBER WOLFE: This is not meant to
7 put you on the spot, but as you know, the Department
8 of Agriculture is seriously considering, we have heard
9 from others, on the verge of, lifting the ban on
10 importation of cattle, beef, from Canada to this
11 country. You've outlined a thoughtful and, I think,
12 careful permit process that affects gelatin, for
13 instance, which would come from a BSE affected region,
14 such as Canada.
15 Do you not think that there is somewhat of
16 a contradiction between being so tight properly and
17 restrictive about allowing gelatin to come in from
18 there, but seriously considering lifting the ban on
19 meat from what would be the first time the United
20 States would ever have lifted a ban that previously
21 existed from a BSE affected country?
22 DR. MORRIS: Yes, sir, the APHIS TSE
23 working group has devised a list of low-risk
24 commodities and a list of mitigation factors under
25 which those low-risk commodities can be imported, the

1 specific criteria under which we would consider
2 accepting these low-risk commodities. That list has
3 been presented through channels to the White House and
4 it is our understanding that the White House has
5 disseminated that list to the trading partners, so it
6 is in negotiation to make sure that all of our trading
7 partners are aware of what the potential actions would
8 be.
9 BOARD MEMBER WOLFE: So you're saying that
10 beef is presumably on a list as a low-risk commodity?
11 Is that what I interpreter you're saying?
12 DR. MORRIS: And I would have to look at
13 the list, but it's specific categories and it's
14 specific ages. And, Lisa, if you want to help me out
15 here? Thank you.
16 BOARD MEMBER FERGUSON: Yes, I'll try and
17 help you out. Speaking for the Department, first of
18 all, I would like to reiterate the point that you
19 probably shouldn't necessarily believe all the rumors
20 that are in the press and everything that you hear.
21 There are lots of things under consideration, not only
22 at USDA, but through the entire Administration, so all
23 of the departments are contributing to these
24 discussions.
25 And the discussions are centered around,

1 you know, is there a science-based way to look at the
2 situation? Are there things that we can do, that are
3 based on known science to address the situation with
4 Canada? And as Terry has described, at least, we, at
5 APHIS, have provided some recommendations for certain
6 products that perhaps could be considered low-risk and
7 could initially be allowed for import under certain
8 conditions.
9 I'm not at liberty necessarily to say what
10 is on that list, what might not be on that list, but
11 we have tried to address it. Okay. First of all,
12 products that are accepted internationally not to
13 present a risk of transmission, obviously, are not
14 affected already. But we are looking at a range of
15 things to say these could be considered lower risk
16 than other things. And really it's a wide ranging
17 list that goes over a lot of issues.
18 BOARD MEMBER WOLFE: Thank you.
19 DR. MORRIS: Thank you.
20 CHAIR PRIOLA: Okay. Thank you very much,
21 Dr. Morris. We'll now move on to the open public
22 hearing portion of the morning. So, Dr. Freas?
23 SECRETARY FREAS: As part of the Advisory
24 Committee program, we hold open public hearings, so
25 that members of the public may wish to make comments

1 to the Advisory Committee will have the opportunity to
2 do so. At this time, I have received two requests.
3 One is a written request. This written request was
4 run off for the Committee members, posted in the
5 viewing notebook out on the table and some copies were
6 provided for the public if you were here early.
7 The second request is from Mr. David
8 Bieging and he is at the microphone right now.
9 Welcome.
10 MR. DWYER: Actually, I'm Dan Dwyer. Dave
11 Bieging made the request and I'm going to speak. I'm
12 Dan Dwyer. I represent the Gelatin Manufacturers of
13 Europe, and I'm also speaking today on behalf of the
14 Gelatin Manufacturers Institute of America. You've
15 already heard from representative of these two
16 associations this morning. These associations
17 represent virtually all of the gelatin produced in
18 Europe and in the United States.
19 These two associations have been working
20 for many years, as you know, to ensure that gelatin is
21 safe and we've been pleased to be able to do so in
22 cooperation with the FDA. As we've discussed with FDA
23 previously, we would like, at this time, to comment on
24 the questions that FDA has asked this Committee to
25 address today.

1 Specifically, FDA's Question 1 currently
2 reads "Do the results of these new studies demonstrate
3 a reduction in infectivity that is sufficient to
4 protect human health?" This question must be
5 interpreted in light of the normal circumstances
6 surrounding gelatin production. In particular, the
7 question focuses only on the manufacturing processes
8 that were studied, but in practice, as you've heard
9 today, the safety of gelatin is based on two
10 principles.
11 The first principle is the use of raw
12 materials. As you know, in Europe this involves
13 controls on raw materials imposed by the European
14 Union and by GME members. The second principle is the
15 use of manufacturing processes that can eliminate any
16 potential infectivity that might theoretically be
17 present in the raw materials. In Europe, this
18 involves the use of the processes that you've already
19 heard discussed today and that have been studied by
20 GME.
21 These two principles of gelatin safety
22 apply as well to all bone gelatin regardless of
23 geographic origin. Therefore, we request that when
24 the Committee considers FDA's Question 1 it take these
25 two principles into consideration, that is we would

1 recommend that the question be revised to read "Based
2 on the use of raw material sources and gelatin
3 manufacturing processes, as described in the
4 information presented to the Committee today, do the
5 results of these new studies demonstrate a reduction
6 in infectivity that is sufficient to protect human
7 health?"
8 FDA's Question 2 addresses the Agency's
9 guidance on gelatin. As you have heard already today
10 from Dr. Potter, in 1997, FDA issued a guidance
11 document that established certain parameters for the
12 sourcing and processing of gelatin in order to avoid
13 BSE risk. At that time, the effect of the gelatin
14 manufacturing process on in infectivity had not been
15 proven. The data discussed with the Committee today,
16 however, in our view, provides a basis for concluding
17 that FDA's guidance is no longer necessary.
18 Indeed, as Dr. Chiu mentioned to you
19 earlier, you may decide that gelatin should be exempt
20 that gelatin should be exempt from any FDA
21 restrictions. At a minimum, we believe that the
22 guidance should be modified so as to improve the
23 opportunity for European raw materials to be brought
24 into compliance with the guidance while at the same
25 time maintaining appropriate controls on the use of

1 European raw materials and, as Mr. Masson expressed
2 before, ensuring a continued adequate supply of
3 gelatin for pharmaceutical use.
4 If the Committee takes the approach of
5 modifying the guidance in this way, we request that
6 the Committee consider two potential modifications to
7 the guidance. The current text of the guidance has
8 been provided already to you by FDA and, indeed, our
9 recommended changes to the text have also already been
10 provided to you for your consideration.
11 First, FDA's guidance currently requires
12 that "cattle come from BSE-free herds." As a
13 practical matter, the term BSE-free herd refers to a
14 herd in which there has not been a single animal
15 identified with BSE. In Europe, it is mandatory, as
16 you've heard, that animals over 30 months of age be
17 tested for BSE, whereas animals under that age are
18 normally not tested, because they have not been
19 defined, at this time, to pose a risk to human health.
20 Thus, in practice, a BSE-free herd is a
21 herd in which BSE has not been detected in tested
22 animals. FDA's guidance in this regard would be
23 clearer if it were to include a brief explanation of
24 the term BSE-free herd by stating "BSE-free herd as
25 determined by generally accepted testing procedures."

1 The second modification to the guidance
2 that we would ask the Committee to consider is one
3 that this Committee has considered before. FDA's
4 guidance currently requires that heads, spines and
5 spinal cords be removed from gelatin raw materials
6 "directly after slaughter." In 1998, this Committee
7 recommended that the removal of spines may be done at
8 any time during the deboning process. Indeed, the
9 removal of heads and spinal cords is not an issue as
10 you heard, because they are already removed before or
11 at the time of slaughter.
12 Therefore, it continues to be appropriate
13 for FDA's guidance to be modified to permit the
14 removal of spines at any time during the deboning
15 process. As the Committee considers FDA's Question 2B
16 then, we request that these proposed modifications to
17 the guidance be taken into consideration. A copy of
18 our recommended changes to the guidance has been
19 distributed to you already for your consideration, and
20 it also has been made available to the public.
21 Thank you very much. We appreciate the
22 opportunity to appear before you today.
23 SECRETARY FREAS: Thank you for your
24 comments. Is there anyone else in the audience who
25 would like to address the Committee, at this time? If

1 not, Dr. Priola, I would like to state that we all
2 have three more open public hearings throughout this
3 meeting, and we do encourage the public participation.
4 Thank you.
5 CHAIR PRIOLA: Okay. So the questions put
6 to us by the FDA are now open for discussion and
7 voting. Do we have the questions to put up? So the
8 first question, while they're getting it up there, is
9 simply, well, hopefully simply, do the results of
10 these new studies demonstrate a reduction in
11 infectivity that is sufficient to protect human
12 health? Are there any comments or any discussion from
13 the Committee? Yes, Dr. Hogan?
14 BOARD MEMBER HOGAN: Since nobody else is
15 biting, let me take this opportunity to say that when
16 I reviewed your article and when I started reading
17 this voluminous amount of material, I sort of looked
18 with the same sort of skeptical eye that I do when I
19 accept papers for publication, and I initially had,
20 when I started reading, several questions about
21 processing and scale-down issues and residual
22 infectivity, etcetera. But as I got deeper and deeper
23 in this, we concur that those had been addressed.
24 So the initial questions that I have asked
25 today, I am extremely personally pleased with the

1 results of these studies. And while no study can be
2 absolutely perfect, and I think that all the questions
3 that the original Committee in 1997 had regarding the
4 data, in my mind, have been answered.
5 CHAIR PRIOLA: Dr. Bailar?
6 BOARD MEMBER BAILAR: I agree that these
7 are very important experiments. They were very well
8 done. I read the reports also as somebody who has
9 done a lot of reviewing. I do have one remaining
10 question or set of questions. I'm not sure that we
11 know enough about the time course of deactivation and
12 why some of the infective agents seem to be so
13 resistent.
14 CHAIR PRIOLA: Well, maybe Dr. Rohwer
15 would like to address that more specifically, but,
16 well, would you, Bob, would you like to, since this is
17 your day. I don't want to speak for you.
18 DR. ROHWER: You're asking a fundamental
19 question of TSE science, actually. And it's something
20 that is going to get a lot of discussion this
21 afternoon. And so I don't know, I mean, I have
22 another talk that I'll be giving and it goes directly
23 to that question, and Robert Somerville has given his
24 perspective on it, and we're going to hear from David
25 Taylor as well. And I think, is there anybody else?

1 I honestly can't remember. Well, and David Asher has
2 some new data on this area as well.
3 And you, yourself, put your finger, I
4 think, on the central issues in your first question to
5 the panel, I mean, to the speakers earlier this
6 morning about the biphasic nature of these
7 inactivations and what is behind them. And we don't
8 know for sure. My own bias is quite different from
9 Robert's. I mean, I don't think there is any
10 intrinsic difference between these agents. What we're
11 talking about is sanctuaries and an inability to
12 actually reach all of the agent. But there are other
13 interpretations.
14 You pointed at one which is a genetic one
15 and there are different ways that you can look at
16 these kinds of protections. We don't have the answers
17 to that. And I think it is a residual question that
18 haunts every single validation study, inactivation
19 study that is done, is to know just how far you can
20 extrapolate this data to zero.
21 I would like to point out that this is not
22 a new issue. It's something that has bedeviled the
23 vaccine industry, water purification, virtually any
24 area in which you want to assure that something is
25 sterile, but you have no way of measuring the entire

1 production lot to find out whether it is or not. And
2 we're kind of in the same boat here.
3 BOARD MEMBER BAILAR: Yes, but I'm not
4 concerned about extrapolating down past the last data
5 point. You have data showing that the curve flattens
6 out, at least, to a considerable extent.
7 DR. ROHWER: Yes, and the point that I'll
8 be making this afternoon is that the place where that
9 flattening out occurs is very context dependent. And
10 you can force it down or up depending on what kind of
11 mixture you are inactivating, what the conditions are
12 and that type of thing. And so the one thing I can
13 say about these studies is that the knowledge that
14 that occurs was part of the design of the study.
15 And your other question about intrinsic
16 versus extrinsic infectivity, the idea that you have
17 to introduce the spike into this spine preparation at
18 the beginning, and you can't know for sure whether you
19 have really mimicked the invito situation in which you
20 would find the infectivity in a BSE infected cow is a
21 very appropriate one. However, in this particular
22 case, I feel more comfortable with it than practically
23 any other study like this that I have done, because it
24 is the spinal cord and the ganglia that we feel are
25 the threat. They are extrinsic to the bone.

1 And what was done here is the stuff was
2 actually injected into the spinal cord and smeared on
3 the bone, actually given an opportunity to dry on the
4 bone, which is something that probably actually
5 happens, and is something that is very, in my opinion,
6 probably very dangerous to do with TSE infectivity.
7 And so the original for the total process experiment,
8 which by the way I wasn't part of the experiment, but
9 nevertheless, my perspective on that is that that was
10 probably just about as good a spike as you could
11 devise. And I mean, I can't think of anything better.
12 You could always argue with the downstream
13 position of spiking homogenate into these things, but
14 even there I think we're talking about a worst case
15 spike in the sense that the homogenate is completely
16 unrefined. And having taken this through the process,
17 you're liable to have stripped away some of the fats
18 and things like that that may be protective to these
19 agents in pure brain type associations. But that's
20 speculation on my part. I can't satisfy your basic
21 underlying concern there, because we don't have data
22 on that point.
23 BOARD MEMBER BAILAR: Well, I remain a
24 little bit concerned, because I recall reading
25 basically in the Daily Press that in the usual method

1 of slaughter, bits of CNS material do get into the
2 peripheral tissues. Is that correct?
3 DR. ROHWER: With penetrating concussive
4 slaughter, I think, it is without a question that that
5 happens. And that's -- I don't want to comment on
6 that. There are people here from the USDA who can
7 probably tell us just whether that practice still
8 occurs there or not. I'm not sure.
9 BOARD MEMBER FERGUSON: I'll answer that.
10 Actually, the issue is with air injected stunning,
11 where you've got a captive bolt and then you've got
12 holes drilled at the end of it, and you inject a bolt,
13 a blast of air, and that type of nomadic air injected
14 stunning is not used in the U.S. industry any more.
15 Our colleagues at the Food Safety Inspection Service
16 are actually in the process of promulgating
17 regulations that officially prohibit that, but based
18 on our understanding of slaughter practices, it is not
19 used in the U.S. Is it used elsewhere?
20 BOARD MEMBER WOLFE: Well, like in the
21 countries where we're talking about, the European
22 countries?
23 BOARD MEMBER FERGUSON: In Europe it also
24 prohibited by regulation within Europe.
25 BOARD MEMBER WOLFE: Within all of Europe?

1 BOARD MEMBER FERGUSON: Yes, yes.
2 Actually, well, within the EU. EU regulations
3 prohibit it. So within the community, I think, you
4 can probably also then assume that any of those
5 countries that are exceeding to the community, the
6 same thing applies.
7 CHAIR PRIOLA: Dr. Somerville, I think,
8 also wanted to address part of your question, Dr.
9 Bailar. Thanks, Bob.
10 DR. SOMERVILLE: Can I just -- is this on?
11 Okay. Just to add to what Bob was saying and to
12 emphasize what I said at the beginning of my talk, was
13 that in processes that were considering its
14 denaturation reaction which is, I suggest, leading to
15 the stabilization of the aging, past the drying
16 processes that Barbara has just mentioned. There are
17 other processes involved in the gelatin extraction
18 procedure which may assist in its destruction or
19 removal.
20 I suggest that possibly there is a degree
21 of hydrolysis of infectivity which would not
22 necessarily depend on the stability of the agent in
23 terms of its denaturation properties, and also, of
24 course, the filtration properties described are of
25 importance in removing, in the totality of the removal


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1 of infectivity from the process.
2 CHAIR PRIOLA: Yes, I think it is also
3 worth remembering that having sat through many of
4 these Committee meetings and always asking for data,
5 I now have before me 2 inches of data, all of which
6 point to the same thing. That in the worst case
7 scenario you can still inactivate these huge doses of
8 infectivity. And then in the real world we're talking
9 about starting material that doesn't even have, at
10 least from the European point of view, as we've heard,
11 since they are now removing the vertebrae, it doesn't
12 even have that material there to start.
13 So whatever contamination may be present
14 is going to be significantly lower than anything that
15 has been discussed here today. So at every step of
16 the process, precautions are being taken that should
17 also be taken into consideration when you're thinking
18 about these things about total inactivation and
19 sequestering evasion.
20 Are we ready to vote, dare I ask? Does
21 anyone else have anything they would like to say now?
22 Shall we call for a vote then?
23 SECRETARY FREAS: There are currently nine
24 voting members at the table. I will go around the
25 table starting with Dr. Johnson over there. Dr.

1 Johnson, how would you like to vote?
2 BOARD MEMBER JOHNSON: I vote yes.
3 SECRETARY FREAS: Dr. Bracey?
4 BOARD MEMBER BRACEY: I vote yes.
5 SECRETARY FREAS: Dr. Ferguson?
6 BOARD MEMBER FERGUSON: Yes.
7 SECRETARY FREAS: Dr. Hogan?
8 BOARD MEMBER HOGAN: Yes.
9 SECRETARY FREAS: Dr. Khabbaz?
10 BOARD MEMBER KHABBAZ: Yes.
11 SECRETARY FREAS: Dr. Priola?
12 CHAIR PRIOLA: Yes.
13 SECRETARY FREAS: Ms. Walker?
14 MS. WALKER: Yes.
15 SECRETARY FREAS: Dr. Wolfe?
16 BOARD MEMBER WOLFE: Abstain.
17 SECRETARY FREAS: Dr. Bailar?
18 BOARD MEMBER BAILAR: No.
19 SECRETARY FREAS: The tally is 7 yes
20 votes, 1 abstain vote, and 1 no vote.
21 CHAIR PRIOLA: Okay. So we can move on to
22 Part A of the second question, which is due to
23 scientific data and information available support the
24 following current FDA recommendation on bone gelatin.
25 And we can keep in mind that we can modify as the FDA

1 has said we can modify this question if we think it is
2 necessary for this recommendation. So that's open for
3 discussion. Dr. Bailar?
4 BOARD MEMBER BAILAR: Before we vote on
5 this, could we have somebody from FDA say whether the
6 modifications suggested are acceptable?
7 CHAIR PRIOLA: I'm sorry, the
8 modifications suggested by the gelatin manufacturers?
9 BOARD MEMBER BAILAR: Yes.
10 CHAIR PRIOLA: Yes. Would someone from
11 FDA, yes, Dr. Chiu.
12 DR. CHIU: I would put the question back
13 to the Committee. If the Committee think, you know,
14 the modification suggested by industry is acceptable,
15 then we will take that recommendation back to the
16 Agency and then have internal discussion.
17 CHAIR PRIOLA: Comments from the
18 Committee? I would like to read through the gelatin
19 manufacturers recommendations. Is there any
20 overwriting reason that anyone can see here to alter
21 what the FDA already has down, which seems to cover
22 what it should in terms of removing risk materials?
23 Dr. Hogan?
24 BOARD MEMBER HOGAN: No, I don't think it
25 should ever go under non-exempt. I think that this is

1 good. The question is from the industry, why is it
2 important to -- when you say BSE-free herds, that
3 covers it. I guess what you're not allowed to use
4 then are herds which contain animals that are younger
5 than 30 months, and you would like to be able to do
6 that. Is that the sense of why you want the
7 modification? Since animals that are less than 30
8 months are already assumed to be BSE-free.
9 CHAIR PRIOLA: Dr. Schrieber, Mr.
10 Schrieber?
11 MR. SCHRIEBER: This request for
12 modification is based of an opinion expressed by the
13 USDA. USDA has stated to FDA we do not consider any
14 herd in Europe being BSE-free. So this means the
15 current text, the way this is written, would exclude
16 altogether all European bones to be used for gelatin
17 manufacturing and then exported into the U.S. So
18 therefore we need the clarifications that under
19 certain circumstances, and that's what we have
20 described, that the animals are tested according to
21 current procedures in Europe, that this would be,
22 let's call it, equivalent to the BSE-free herds. So
23 that's one point.
24 And the other request for the modification
25 is what I said before. Due to the transport of the

1 carcasses from a slaughter house to a meat packer to
2 sausage companies, with bone in, if the request will
3 stay, removal of spine, I'm not talking about spinal
4 cord, this is directly removed after slaughter. But
5 removal of spine has to be taking place directly after
6 slaughter, this would as well totally exclude the use
7 of European bones, because this is not the standard
8 procedure.
9 So we need some time frame during the
10 further processing, because deboning is done somewhere
11 else and transport of carcasses without the bones is
12 not possible. This is the ratio behind our request.
13 BOARD MEMBER HOGAN: Well, then I would
14 ask Lisa, is that true the USDA considers no herds in
15 Europe BSE-free, despite testing?
16 BOARD MEMBER FERGUSON: Well, I think what
17 we're dealing here with is the way our regulations are
18 written. And our regs prohibit the entry of ruminant
19 from any country that is on the BSE restricted list.
20 So, you know, since our regs are clearly prohibiting
21 all these animals, we can't necessarily make an
22 exemption and say yes, okay, something is free,
23 something is not free.
24 CHAIR PRIOLA: I'm sorry. Dick, go ahead.
25 BOARD MEMBER JOHNSON: Yes. If this were

1 modified by this Committee, that would not affect the
2 FDA regulations, and then you would have two
3 conflicting rules, right? Is that right?
4 CHAIR PRIOLA: Well, you're not
5 necessarily going to have two conflicting rules. You
6 know, the way our regs are written, we prohibit
7 gelatin from entering, as Dr. Morris has described,
8 unless it can be demonstrated that it is not going to
9 go for animal use. Okay.
10 BOARD MEMBER FERGUSON: So we don't make
11 this type of an exemption, you know, for stuff going
12 for animal use, if that's clear.
13 BOARD MEMBER JOHNSON: I thought it was
14 all products derived from cattle that were from BSE
15 positive countries that you don't permit. But as long
16 as we eat it, it's all right? As long as humans eat
17 it.
18 BOARD MEMBER FERGUSON: APHIS' authority
19 is related to animal health issues. APHIS' authority
20 is not related to public health issues, so our regs
21 are written based on that authority.
22 BOARD MEMBER JOHNSON: But doesn't your
23 animal health issue say that products derived from,
24 cattle products derived from BSE positive countries
25 cannot be brought into the country?

1 BOARD MEMBER FERGUSON: Correct. Our regs
2 in general prohibit not just bovine products, but most
3 ruminant products.
4 BOARD MEMBER JOHNSON: Yes.
5 BOARD MEMBER FERGUSON: From countries on
6 our BSE restricted list. However, I think, as Dr.
7 Morris explained in her presentation, there are
8 certain things in the regs that can be allowed entry
9 and one of those things is gelatin under certain
10 conditions that is not going for animal use.
11 BOARD MEMBER JOHNSON: That's in your
12 exemptions at FDA?
13 BOARD MEMBER FERGUSON: Correct.
14 CHAIR PRIOLA: This is USDA, Dick, so,
15 yes. They are USDA.
16 BOARD MEMBER JOHNSON: USDA, that's okay.
17 CHAIR PRIOLA: Yes, the FDA is strictly
18 concerned with oral or topical applications in humans
19 of gelatin, so the USDA regs aren't our concern. It's
20 the FDA. It's this specific recommendation by the
21 FDA.
22 BOARD MEMBER JOHNSON: Except it isn't --
23 wouldn't it be a regulation, for instance, that you
24 couldn't bring in cattle hides from Europe under the
25 safety of animals?

1 BOARD MEMBER FERGUSON: No, hides and
2 skins are exempted from our regs.
3 BOARD MEMBER JOHNSON: They are exempted?
4 Okay.
5 BOARD MEMBER FERGUSON: They are
6 considered, yes, not to present a risk of
7 transmission.
8 BOARD MEMBER JOHNSON: Okay.
9 CHAIR PRIOLA: Dr. Bailar?
10 BOARD MEMBER BAILAR: How is herd defined?
11 Is that all the animals on a single farm or ranch?
12 BOARD MEMBER FERGUSON: I don't know why
13 you guys are looking at me, because these aren't our
14 regs. Actually, I have to admit, I mean, these are
15 the types of things that you always run into when you
16 put that type of a thing in a reg. It's very
17 difficult to define that. When we look at it from an
18 animal health point of view, it's a group of animals
19 that is housed together. And if a premise has, you
20 know, two separate groups of animals that never come
21 into contact with each other and are managed
22 completely differently, those could, technically, be
23 considered two different herds. But essentially, it's
24 a group of animals that are managed together and
25 handled together.

1 BOARD MEMBER BAILAR: Okay.
2 CHAIR PRIOLA: Mr. Dwyer has been standing
3 there for a couple of minutes. Would you like to make
4 a comment?
5 MR. DWYER: Yes, thank you. As you've
6 explained, there is a complete distinction between the
7 FDA's guidance and the USDA's regulations. The USDA's
8 regulations are intended only to protect animals and
9 not to deal with anything that the FDA has going on
10 here. If you go back and look at the early meetings
11 and transcripts of this Advisory Committee when FDA
12 was discussing with the Committee the formulation of
13 this guidance, you'll see that the requirement for
14 BSE-free herd restriction was put in as one of a
15 series of restrictions in FDA's guidance that were
16 intended to protect the safety of gelatin.
17 There wasn't much discussion, at that
18 time, of what a BSE-free herd meant or how that would
19 be defined. Because it is obviously possible to
20 define it in many different ways, what the industry
21 was looking for is a way of defining it in a logical,
22 rational way that is consistent with current practice
23 in Europe. And that's basically it.
24 BOARD MEMBER BRACEY: Although --
25 CHAIR PRIOLA: Go ahead.

1 BOARD MEMBER BRACEY: Although I think the
2 safety of gelatin has been certainly demonstrated to
3 be rather robust today, what bothers me is, in
4 essence, a disconnect between two levels of animals.
5 One is the human where we are considering saying that
6 well, it's okay, based on the data that we see, to
7 allow humans to ingest these materials. Whereas, on
8 the other hand, another arm of the Government says
9 that another animal, which some of us think would be
10 on a lower level perhaps than the human, that it is
11 not acceptable.
12 And, you know, I really feel that we need
13 to have some sort of harmonization, because the
14 message, I think, that -- if I were the public, I
15 would be somewhat concerned about the message that we
16 would be issuing.
17 BOARD MEMBER FERGUSON: Yeah, that's a
18 valid point. I would ask everybody, however, to keep
19 in mind that, you know, it's one thing to talk about
20 an agent that is coming from cattle and going directly
21 back into cattle versus an agent that is coming from
22 cattle and is going into a different species.
23 Granted, it has been demonstrated that there is that
24 transmission, but you do still have somewhat of a
25 species barrier there.

1 CHAIR PRIOLA: Dr. Khabbaz?
2 BOARD MEMBER KHABBAZ: Yeah, and actually,
3 listening to the USDA presentation, I have that same
4 reaction saying there is an apparent contradiction
5 here between conditions for animals and humans. But
6 in thinking about it, I mean, you have a potential
7 amplification. I mean, these are some different
8 issues that go into place with animals and that's why
9 I didn't comment. But there is an apparent
10 contradiction. I agree.
11 CHAIR PRIOLA: Yes, Lisa?
12 BOARD MEMBER FERGUSON: Can I go back to
13 the term BSE-free herd? That's very difficult to
14 define and I don't want to necessarily sound too
15 harsh, but in some ways it is sort of meaningless. I
16 know we have struggled with those types of definitions
17 as we tried to setup our scrapie or CWD eradication
18 programs. And, you know, specifically, as we're doing
19 our CWD program, we don't necessarily define under the
20 auspices of that program as herd as free until they
21 have gone through a 5 year period with extensive
22 surveillance and a lot of that. So it is a bit
23 difficult to define.
24 I guess I'm not quite sure exactly what
25 level of risk mitigation it's necessarily adding in

1 this guidance. Probably more of the risk mitigation
2 is coming from removing those tissues that are at
3 highest risk and also just through the inactivation of
4 the process itself. So perhaps what we should
5 consider is that specific point even necessary in
6 there or does it just cause more confusion than it is
7 really worth?
8 CHAIR PRIOLA: Dr. Bailar?
9 BOARD MEMBER BAILAR: I feel like I just
10 don't know enough about all this. And I am concerned
11 about the definition of a herd. Does this include
12 animals that come from the same source, prior to the
13 time they are parceled out into different farms? Does
14 it include any element of time? That is, you know, if
15 all those animals there today are gone and you bring
16 in new ones, is that part of the same herd? What
17 about overlap in time, which I understand is common in
18 the industry, that there is a continuing flow of young
19 ones in and older ones out. I just don't know enough
20 about it.
21 CHAIR PRIOLA: Dr. Chiu, do you want to
22 comment on what the FDA means by BSE-free herd or is
23 there something more specific you can tell us?
24 DR. CHIU: Well, I will try. If I didn't
25 get the picture across right, then I will ask Dr.

1 David Asher to add it. I think in our original
2 discussion we were thinking a herd is a group of
3 animals managed, you know, by the same people and also
4 physically they are together, so they are sort of
5 separated from another group of animals. And also we
6 think when we say BSE-free means, you know, that group
7 of animals in the past there was never, you know, a
8 BSE case among that group. In addition, we were also
9 thinking, you know, that group of animals were never
10 fed with meat and bone marrow, so therefore they don't
11 have that kind of risk to contact BSE.
12 CHAIR PRIOLA: Dr. Wolfe, did you want to
13 say something?
14 BOARD MEMBER WOLFE: I just wanted to ask
15 Lisa, just from your perspective, what do you think
16 the difference is between this guidance or
17 recommendation as it now exists and the way that the
18 industry would like to redefine it? I mean, the
19 reason I'm asking you is (a) you're from the USDA, but
20 (b) you have just gotten done saying you don't think
21 the phrase herd has any meaning at all. So if it
22 doesn't have any meaning, then what is the difference
23 between our current version and what they propose?
24 BOARD MEMBER FERGUSON: That's a good
25 point, and actually I don't really see a whole lot of

1 difference in true meaning between what the industry
2 has proposed and what currently exists. My sense of
3 what industry has proposed is trying to make it more
4 realistic and to make it more meaningful in what fits
5 with industry practices, which is a very valid point,
6 especially this one about the removal of tissues and
7 where.
8 BOARD MEMBER WOLFE: I'm specifically just
9 talking about the herd definition.
10 BOARD MEMBER FERGUSON: Actually, I mean,
11 after what Dr. Chiu has just said, you know, if those
12 are the specific issues that FDA is intending to
13 address with that point, then I guess my suggestion
14 would be to put that in there as the guidance to say
15 that these animals have not been fed meat and bone
16 meal, those types of things. That is a more accurate
17 definition of the risk mitigation measure and is more
18 easily understandable and leads to less confusion.
19 CHAIR PRIOLA: Looking though this, I
20 don't have any trouble. I think that's an excellent
21 suggestion actually for the FDA to modify it according
22 to what they mean by BSE-free herd. The other
23 suggested modification by industry down there at the
24 bottom, I'm somewhat uncomfortable with, but you had
25 mentioned that you weren't as uncomfortable. Why

1 exactly is that?
2 BOARD MEMBER FERGUSON: Well, I think
3 that's probably just because of my understanding of
4 slaughterhouse practices. And if this is saying, you
5 know, as it currently says, let me find it, "and if
6 the slaughterhouse removes the heads, spines and
7 spinal cords directly after slaughter," that lends
8 itself to a lot of interpretation.
9 First of all, talking about spine directly
10 after slaughter, does that mean right after the animal
11 is stunned and, you know, hung up on the rail and bled
12 out? if so, that's not necessarily common practice.
13 You need that vertebral column there to give some
14 structure to the carcass that's moving through the
15 plant. You know, and I think the point is that those
16 tissues are removed at some point in time during the
17 process. Although they are not going into the start
18 of the gelatin manufacturing process. It's not as
19 much a point as specifically when are they removed,
20 it's that they are removed.
21 CHAIR PRIOLA: Which the current guidance
22 says anyway. I mean, I don't see where the industry
23 modification makes that much of a difference if, in
24 fact, they take that out at the level of the
25 slaughterhouse they take out that requirement. The

1 way I read it.
2 BOARD MEMBER FERGUSON: Well, I guess from
3 an interesting point of view and actually let me
4 rephrase that. From a Government point of view, as a
5 federally employed Government veterinarian that might
6 be put in a position to certify to this, I probably
7 couldn't. And it is just because of the way that that
8 is worded, where this stuff is removed directly after
9 slaughter.
10 CHAIR PRIOLA: Where does it say directly
11 after slaughter?
12 BOARD MEMBER FERGUSON: Right in the text,
13 yes. If the slaughterhouse removes the head, spines
14 and spinal cords directly after slaughter.
15 CHAIR PRIOLA: I just have after
16 slaughter. Do I have the wrong one?
17 BOARD MEMBER FERGUSON: Can we put it up?
18 CHAIR PRIOLA: Oh, I see. You're looking
19 in the -- I see. It says directly after slaughter if
20 it's from a BSE herd. Later in the recommendation it
21 says if the slaughterhouse removes after slaughter.
22 So there is two different ones.
23 BOARD MEMBER FERGUSON: Yes, but even, I
24 mean, the later one remove head, spines and spinal
25 cords as a first procedure following slaughter, that

1 just leaves open a lot of ambiguity and, you know,
2 there are some of our folks who are very literal, you
3 know, when they would read that and say oh, no, they
4 didn't, you know, stun this animal, bleed her out and
5 then immediately remove things, therefore, I can't
6 attest to that type of certification.
7 CHAIR PRIOLA: I guess again, could we ask
8 FDA, is there -- since that's a USDA interpretation of
9 this recommendation, does the FDA have the same sort
10 of reservations or are they concerned about those same
11 sort of reservations as to when exactly the tissue is
12 taken after slaughter or is the discussion enough?
13 DR. ASHER: No, I think the discussion is
14 very useful. My recollection of the intent of the FDA
15 with both those issues was that the reason why BSE-
16 free herds was specified but not defined was just to
17 put the industry on notice that under no circumstances
18 did we consider material from a herd recognized to
19 have BSE as being an acceptable source for any kind of
20 gelatin entering the United States. No effort at the
21 time was made to define a BSE-free herd.
22 If one were to try to define an acceptable
23 BSE-free source, I would certainly agree with Dr. Chiu
24 that it would not simply be all tests of 30 month old
25 animals going to slaughter are negative. The herd

1 would have to have a certified history of never using
2 food supplements containing prohibited proteins.
3 There would have to be an adequate surveyance program,
4 not just 30 months slaughter animals.
5 And my personal opinion would have to
6 include a sufficient number of older sentinel animals
7 and, of course, careful veterinary surveyance to make
8 sure that all sick animals were recognized. My
9 personal opinion also is that this Committee not
10 entertain an assertion that an animal that tests
11 negative at 30 months poses no threat to the public
12 health. I say both those things without attempting to
13 influence the discussions of the Committee. Thank
14 you.
15 CHAIR PRIOLA: Would it be sufficient to
16 say something like a BSE-free herd is defined by the
17 FDA, if that is in fact defined somewhere, clearly?
18 DR. CHIU: No, we have not put in writing.
19 And regarding the slaughter, you know, the first
20 procedure are directly after slaughter, I remember our
21 discussion in the past, was because if you remove
22 spinal cord, it is not possible, you know, to make
23 sure entire cord, everything is removed. You might
24 have residual, you know, tissues. And if you carry
25 that to somewhere else and then remove the spine, then

1 create contamination of other tissues, in the bones of
2 other tissues. So we thought, you know, it would be
3 better to remove, you know, the spine, the vertebrae
4 at the slaughterhouse. That was the thought at that
5 time.
6 CHAIR PRIOLA: I guess the other thing to
7 consider is, again, given all the data we have seen
8 showing inactivation of infectivity following the
9 gelatin extraction process, the issue of
10 contamination, cross-contamination by a spinal cord
11 being removed at a different part of the slaughter
12 process may not be as major an issue given the fact
13 that now there are these five individual studies, all
14 of which saying that the gelatin process itself, as
15 you get to the end, can remove extremely high levels
16 of infectivity under worst case conditions. So it's
17 possible that this discussion as to when things are
18 removed and may not, given that data, be as critical
19 as it might have been before we had access to this
20 data. Dr. Bailar?
21 BOARD MEMBER BAILAR: Dr. Priola, we have
22 had questions about some of the wording in this
23 recommendation, this draft recommendation. I have a
24 question about the last sentence that the processors
25 are responsible for the safety of what comes into

1 them. Without offering any guidance about that, would
2 it be appropriate? I don't want to vote against this.
3 On the other hand, I'm not very comfortable about
4 voting for it.
5 Would it be appropriate to defer action
6 until the next meeting with a request that FDA
7 consider revising the wording? I think the intent is
8 fine. I have no particular quarrel with the intent of
9 the changes proposed by the industry, but I think it
10 needs some tightening up.
11 CHAIR PRIOLA: Well, I think in a way
12 that's what the FDA is actually asking us to discuss.
13 Given what we have heard today and the current
14 discussion, how can we modify this or should we modify
15 it in a way that addresses the concerns of the
16 Committee? So this, I would think would be an
17 opportunity to make that known, how you would want to
18 do that.
19 BOARD MEMBER BAILAR: I'm not sure we can
20 modify it on the fly this way. That's why I would
21 like to allow a little bit of time for people who know
22 a lot more about the process, the problems, than some
23 of us on the Committee, and time for some reflection
24 about the implications of any changes.
25 BOARD MEMBER WOLFE: I would agree with

1 John, because I think based on what Lisa has said,
2 which, I think, amplifies the understanding of the
3 process somewhat and what other people are saying,
4 that the FDA has gotten some input from us, which is
5 what Question 2B is, and it would make most sense for
6 us to get at the next meeting the new version of the
7 recommendation to vote on.
8 CHAIR PRIOLA: Do you have suggestions for
9 changes that we can make? I mean, we still have to
10 actually vote on Question 2A, but would you have
11 suggested for recommendations?
12 BOARD MEMBER WOLFE: I mean, defining, as
13 Lisa suggested, what a BSE-free herd is, sorting out
14 the differences between directly after, immediately
15 after, first process or just after. I mean, there are
16 three different ways of describing in the current
17 recommendation the timing between slaughter and
18 removal of spine, spinal cord and so forth, so I
19 think, I mean, those are, I think, two areas that need
20 to be neatened or tightened up.
21 CHAIR PRIOLA: Yes. Dr. Khabbaz?
22 BOARD MEMBER KHABBAZ: Yes, it's a
23 question to the FDA. Can we vote on this
24 recommendation and then leave to the FDA to wordsmith
25 the BSE-free herd and the timing of removal based on

1 the discussion that they heard?
2 DR. CHIU: I think we definitely can go
3 back to before BSE-free herd, you know. We have some
4 idea, you know, over the years, you know, we have in
5 mind. We would like to get advised whether to remove
6 the spinal, the spine, the vertebras in the
7 slaughterhouse is needed or not because of the results
8 you have seen, you know, from the validation studies.
9 CHAIR PRIOLA: Dr. Hogan?
10 BOARD MEMBER HOGAN: Well, it seemed, the
11 validation studies suggested if you can start with
12 really high titre material, that you get rid of
13 almost, I mean, virtually totally. So I think what
14 you start with in the real world is sort of
15 irrelevant, because it's never going to be as high as
16 what they are starting with in these validation
17 studies.
18 Now, I am a little concerned that if you
19 leave the spinal cord in and then you drive, you know,
20 200 miles to have the spinal cord removed, it is going
21 to dry during that time period. Is that going to
22 sequester some agent that might be more difficult to
23 remove later? But as I just said, I think the titres
24 will be much less than the validation studies. So I
25 personally wouldn't have a problem with that.

1 CHAIR PRIOLA: Mr. Dwyer, do you have a
2 brief comment?
3 MR. DWYER: Thank you. Just as a
4 reminder, this Committee voted in 1998 to agree with
5 or recommend to FDA the removal of the spines in the
6 manner that we have suggested in our draft
7 modifications to the guidance. We have attempted to
8 craft our draft modifications to the guidance with
9 respect to this issue, that is spine removal in a way
10 that is consistent with what this Committee
11 recommended in 1998 as reflected in the transcript of
12 the meeting from April 1998. Thank you.
13 CHAIR PRIOLA: Dr. Johnson and then Dr.
14 Ferguson.
15 BOARD MEMBER JOHNSON: Well, I think it's
16 very impressive how much this does decrease the
17 infectivity. On the other hand, we should go back to
18 remember that there is that inactivated tail or
19 whatever you want to call it, so there is inactivated
20 particles, and think back to the Committee hearings
21 after the Cutter episode with Jonas Salk where they
22 forgot, they neglected looking at the unneutralized
23 tail, which caused the whole Cutter episode.
24 Is it there and I think we should consider
25 that. I don't think that's enough to change the

1 rules, but I don't think it's enough to say well,
2 let's not worry about splashing a little spinal cord
3 around. I think we still ought to keep that as tight
4 as absolutely possible to keep the contamination
5 membranes of the spinal cord down.
6 So I would agree that I don't think we
7 need to change. I voted yes on 1, but on this I would
8 not want to see it made more permissive for the
9 possibility of contamination despite the good
10 inactivation studies.
11 BOARD MEMBER FERGUSON: I guess I would
12 like to briefly run through sort of the standard
13 slaughter practice at least in the U.S., and ask
14 everybody to sort of think about the possibilities for
15 contamination. You know, an animal comes in. It is
16 stunned, rendered unconscious, then, essentially,
17 hooks are applied to the rear legs and it is bled out.
18 The animal is skinned. The head is removed and then,
19 generally, the carcass is split, at that point in
20 time.
21 The standard practice is to go ahead and
22 remove the spinal cord, at that point in time. That
23 is the easiest time to do it. But the issue is not
24 necessarily the removal of the cord. The issue is the
25 removal of the spine and that, you know, vertebral

1 structure that allows the carcass to sort of hold
2 together and it's going through the rest of the
3 processing process.
4 So if concerns are about cross-
5 contamination from removal of the vertebral column
6 later in the process, I'm not quite sure where that
7 cross-contamination is going to come from, especially
8 on bones and bone chips that are going into a gelatin
9 derived process, because even if you assume okay, you
10 can get some contamination when you split that carcass
11 in half or if you have a missplit, you're getting
12 aerosolized cord that is going on the surface of that
13 carcass, and the bones aren't on the surface of that
14 carcass. The meat on those bones is removed elsewhere
15 in the meat cuts, and the contamination isn't
16 necessarily going to be on those bones, per se, which
17 is what is going into the gelatin process.
18 CHAIR PRIOLA: I think we could -- at
19 least, the sense I'm getting is the recommendation as
20 it stands needs some tightening up in terms of
21 clarifying definitions of BSE herd and when after
22 slaughter things need to be removed. The primary
23 question prior to this is do the scientific data and
24 information available support the following FDA
25 recommendation? If the answer is no, what changes?

1 Are there changes other than tightening up these
2 definitions that anyone would like to recommend?
3 For myself, the removal of the vertebral
4 column, I think, is a big issue for European countries
5 because of the European BSE, but given that here in
6 the United States there is as yet no BSE and they
7 haven't yet moved, if I remember correctly from this
8 morning, to removal of the entire vertebral column, is
9 that right, that has happened. There is a
10 significantly different level of risk, if I understand
11 correctly. So these rules seem to apply to really
12 primarily European BSE countries.
13 Should we call for a vote on Part 2A and,
14 if necessary, move on to Part B with specifics? Are
15 there any objections to that? If the FDA has gotten
16 what they need from the discussion, which I think they
17 have, we can move on to a vote for 2A.
18 SECRETARY FREAS: I will go around and
19 poll the table exactly as last time. Dr. Johnson?
20 BOARD MEMBER JOHNSON: With the likely
21 changes made by FDA, do we vote yes or no?
22 CHAIR PRIOLA: I think you vote no.
23 BOARD MEMBER JOHNSON: You vote?
24 CHAIR PRIOLA: And then we ask what
25 changes for 2B. Isn't that right? Well, actually, I

1 think yes. Well, because I think that the
2 scientific --
3 BOARD MEMBER JOHNSON: I would vote.
4 CHAIR PRIOLA: Yes.
5 BOARD MEMBER JOHNSON: If I looked at that
6 just as it says, which states there on the board, my
7 answer would be yes.
8 CHAIR PRIOLA: Yes. I think you can vote
9 yes or no and we can still make modifications in 2B,
10 because this Committee has never hesitated to make
11 modifications.
12 BOARD MEMBER JOHNSON: Then my vote
13 stands, Sue.
14 CHAIR PRIOLA: So I'm sorry, so what is it
15 again, Dick, officially?
16 BOARD MEMBER JOHNSON: It's a yes.
17 SECRETARY FREAS: Dr. Bracey?
18 BOARD MEMBER BRACEY: I would second that
19 yes.
20 SECRETARY FREAS: Dr. Ferguson?
21 BOARD MEMBER FERGUSON: Yes.
22 SECRETARY FREAS: Dr. Hogan?
23 BOARD MEMBER HOGAN: Yes, but we need
24 modification.
25 SECRETARY FREAS: Dr. Khabbaz?

1 BOARD MEMBER KHABBAZ: Yes.
2 SECRETARY FREAS: Dr. Priola?
3 CHAIR PRIOLA: Yes.
4 SECRETARY FREAS: Ms. Walker?
5 MS. WALKER: Abstain.
6 SECRETARY FREAS: Dr. Wolfe?
7 BOARD MEMBER WOLFE: No.
8 SECRETARY FREAS: Dr. Bailar?
9 BOARD MEMBER BAILAR: No.
10 SECRETARY FREAS: The industry, would you,
11 please, express your comments on this? Okay. Out of
12 the nine voting members at the table, we have 2 nos,
13 1 abstention and 6 yeses.
14 CHAIR PRIOLA: Okay. Under the part of
15 2B, even though we answered yes, if I tallied right,
16 there are three specific things that we would ask the
17 FDA to clarify. And that would be the definition of
18 a BSE-free herd, to make the recommendations at
19 slaughter, directly after slaughter, you know, just
20 after slaughter, if they could be more specific as to
21 when the vertebral column should be removed, and also,
22 Dr. Chiu had asked specifically about whether removal
23 of the vertebral column is necessary. They wanted
24 some clarification on that, too, I believe. Are there
25 any comments, Dr. Bailar?

1 BOARD MEMBER BAILAR: I would add a point
2 also about some clarification about the insurance by
3 the processors that their supplies are adequately
4 protected.
5 CHAIR PRIOLA: Well, I think that -- isn't
6 that in the last? That is in the last sentence,
7 right, gelatin processes should ensure?
8 BOARD MEMBER BAILAR: It says the
9 processors should ensure, and I would like to know
10 more about that.
11 BOARD MEMBER HOGAN: Well, unfortunately,
12 Dr. Gambetti isn't here, but from my experience in
13 removing spinal cords, there can be left dorsal root
14 ganglia and other nervous tissues depending on how you
15 do it. So I think the issue of vertebral column if
16 you're asking just for some comments, may be important
17 if you want to reduce that last little bit.
18 CHAIR PRIOLA: Does anybody want to
19 recommend any specific language if we can, I don't
20 know if we can, to give the FDA some further guidance?
21 You know, for example, industry recommendation for
22 BSE-free herd. Is that an appropriate way to qualify
23 it, to introduce the concept of testing according to
24 standard procedures? Lisa?
25 BOARD MEMBER FERGUSON: I guess I'm

1 uncomfortable with having testing in there as the only
2 thing that's qualifying the herd. You know, I don't
3 think that testing is necessarily the critical thing
4 to hang your hat on. I think the point is lack of
5 exposure, and that should probably be where that
6 definition heads.
7 CHAIR PRIOLA: Are there any other
8 comments as to specificity as to modifications of the
9 recommendation? Okay. Sidney, do you have anything
10 in terms of the slaughterhouse issue directly after?
11 I mean, how specific should specific be, given again
12 all the data we have heard this morning?
13 BOARD MEMBER WOLFE: No, I understand
14 that, but, I mean, we heard that there is a vastly
15 different slaughtering process in Europe versus here,
16 so what I thought I heard this morning from the
17 Europeans was that since it's done in a different
18 place, it's not even within the slaughterhouse. I
19 mean, is that correct? I mean, in Europe, you just
20 repeat what you said is the main difference between
21 European slaughtering techniques in terms of bone, in
22 terms of getting the bone for gel, as opposed to this
23 country?
24 MR. SCHRIEBER: The difference is only the
25 place of the removal of the bones.

1 BOARD MEMBER WOLFE: The place, right.
2 MR. SCHRIEBER: Just the place.
3 BOARD MEMBER WOLFE: So it's not --
4 MR. SCHRIEBER: Slaughtering practice is
5 exactly the same, I think.
6 BOARD MEMBER WOLFE: But in one case, in
7 this country, the removal of the bones is in the
8 slaughterhouse and there, somewhere else? That's the
9 difference. So it's the issue of transport and
10 whatever. So it's beyond just where in the
11 slaughterhouse. It's in the slaughterhouse or not.
12 The issue is whether we think that it's okay for --
13 which is the issue the industry raised, whether we
14 think it's okay for the bone removal to be somewhere
15 else with at least risks to workers and others that
16 are different than they would be if it were all done
17 within the slaughterhouse.
18 CHAIR PRIOLA: Go ahead.
19 MR. SCHRIEBER: In addition to this, the
20 places of the removal, which other meat processes are,
21 are exactly under the same supervision of the
22 authorities of the public like the slaughterhouse
23 itself. They are meat processors, so they have to
24 follow the same rules. It's just a question of
25 distance. It's not a question of how procedures are

1 done, whether they are inspected, whether they are
2 controlled. That's all the same whether it's here or
3 there.
4 CHAIR PRIOLA: Are there any other
5 comments? I guess I should ask the FDA. Do you have
6 sufficient information in terms of what the Committee
7 is asking for, for modification to the recommendation
8 based on the discussion and what was just said?
9 DR. CHIU: Well, in my mind, I'm still not
10 quite clear, you know. We have read and heard, you
11 know, the study results and as many of you expressed,
12 it's quite impressive. So I am not quite clear, you
13 know, whether we get any advice. Is it necessary to
14 remove spine and if it's necessary, then when it
15 should be done? So if we can, you know, have a little
16 more discussion whether the spine, the vertebrae,
17 actually needs to be removed.
18 CHAIR PRIOLA: Lisa?
19 BOARD MEMBER FERGUSON: Yes, I guess I'll
20 throw my two cents worth in here and everybody else
21 can have at it. I guess, I think it's important to
22 essentially limit the use of vertebral column in the
23 production of gelatin or say, you know, you are not
24 using vertebral column in the production of gelatin.
25 I don't think it makes any difference where or when

1 that is removed, but to say yes, it's not included,
2 it's not going into the gel balm is important.
3 CHAIR PRIOLA: Yes, I would actually agree
4 with that, that it's important that it is being
5 removed given the data where heard. Where exactly
6 it's removed may not be that big of an issue since you
7 can activate, apparently, quite effectively quite a
8 bit of infectivity that might be residual on the bone
9 surface after removal of the spinal cord.
10 I am actually comfortable if the FDA does
11 tighten up the definition of BSE-free herd. I am
12 comfortable for myself with the recommendation, how it
13 sits, with just some tightening up of those
14 definitions, BSE-free herd, as well as being careful
15 when you describe when the vertebral column should be
16 removed after slaughter. I think in Europe, all the
17 vertebral columns are removed anyway, so that is moot.
18 It's just where the removal is, and that is not a
19 primary concern for myself.
20 Would anybody else like to contribute? Is
21 it just too near to lunch? Are we running out of
22 steam? Well, if anyone has any -- I mean, so I guess
23 we have addressed the questions and if anyone else
24 would like to say anything after lunch, feel free to
25 do that. When we restart the session at 1:30, 1:40?

1 SECRETARY FREAS: Let's try 1:30.

2 CHAIR PRIOLA: Okay. Let's go for 1:30.

3 (Whereupon, the hearing was recessed at

4 12:45 p.m. to reconvene at 1:37 p.m. this same day.)

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1 A-F-T-E-R-N-O-O-N S-E-S-S-I-O-N
2 1:37 p.m.
3 SECRETARY FREAS: Okay. Thank you very
4 much for rushing through lunch. In the afternoon, we
5 are very fortunate. We will be joined by four new
6 temporary voting members. I would like to go around
7 and introduce them. I won't introduce the whole
8 table, just the four new temporary voting members.
9 Well, I will introduce at least three of the new
10 temporary voting members.
11 On the far side of the table is Mr. Terry
12 Rice, Board of Directors, Committee of 10,000 from
13 Windham, Maine. Would you raise your hand, Mr. Rice?
14 At the corner of the table right in front of the
15 screen is a new voting temporary member for today, Dr.
16 Charles Edmiston. He is associate professor of
17 surgery, Medical College of Wisconsin, and he is also
18 chair of the CDRH General Hospital in Personal Use
19 Device Panel, and he will be taking these issues from
20 today to his center's panels.
21 And we will be very shortly joined by Dr.
22 Kenrad Nelson, who will be sitting next to Dr. Priola,
23 our Chair, and Dr. Nelson is a professor, Department
24 of Epidemiology, Johns Hopkins University School of
25 Hygiene and Public Health, and he is chair of the

1 Center of Biologics Blood Products Advisory Committee.
2 And there is one more person, and that is
3 also from the Blood Products Advisory Committee. That
4 is Dr. David Stroncek, Chief Lab Service Section,
5 Department of Transfusion Medicine, NIH. And to all
6 four of you, I would like to welcome you to the table
7 and thank you.
8 CHAIR PRIOLA: Okay. We'll go on to
9 starting with Topic 2, which is BSE in Canada, and I
10 want to let the Committee know that this is an
11 informational topic only. It's for our benefit.
12 We're here to listen, and there are no questions being
13 posed to us. This is an informational topic only.
14 The first speaker is Dr. Jay Epstein from FDA.
15 DR. EPSTEIN: Thank you, Dr. Priola.
16 Before Mr. Hills makes a presentation on what is known
17 about the reported case of BSE in Canada, I would just
18 like to take a moment to make a brief statement about
19 FDA's current thinking in regard to potential
20 implications of that case report for blood safety
21 policy.
22 FDA is undertaking an assessment of the
23 BSE exposure risk to blood donors in the U.S. and
24 Canada in light of the single BSE case that has
25 recently been reported in Canada. Although, it is

1 premature for the FDA to present any results of this
2 assessment now, we believe that the likelihood of
3 exposure to the BSE agent for both Canada and the U.S.
4 is and has been very small.
5 The exact magnitude of BSE risks for
6 Canada and the U.S. will be difficult to quantify
7 because of methodological limitations. However,
8 preliminary considerations suggest first that the risk
9 of exposure of blood donors in North America to the
10 BSE agent has been extremely low and is even lower now
11 than it was several years ago. And then secondly, in
12 particular, implementation of the feed ban of 1997
13 both in the U.S. and in Canada significantly reduced
14 the likelihood of human exposure to the BSE agent for
15 both countries.
16 FDA does not believe that there are
17 sufficient data, at this time, to warrant changing our
18 blood donor deferral guidance. However, we will
19 continue to study this issue and will take further
20 action as appropriate. Thank you very much.
21 BOARD MEMBER WOLFE: I have a question.
22 CHAIR PRIOLA: Dr. Wolfe?
23 BOARD MEMBER WOLFE: Given that the
24 spectrum of countries for which there are limitations
25 on blood donation go from UK, lots of cases, to EU

1 with some countries with very small numbers of cases
2 in just cattle, and that Canada is still a "moderate
3 risk country" that has had a case, the benefit risk
4 equation is always important, and have you at least
5 tried to get some data, so that this question can be
6 answered better later as to what fraction of the blood
7 supply in this country would be affected if there was
8 some sort of constriction on the ability of people who
9 have spent whatever amount of time in Canada?
10 Is there at least some effort to collect
11 that, because otherwise, as we learn more about the
12 possible risk, small though it may be, and the
13 benefit, which is having a blood supply that is not
14 impaired some comes up to it? So just a simple
15 question. Is someone trying to get a hold of those
16 kinds of data?
17 DR. EPSTEIN: Yes, Dr. Wolfe. Thank you
18 for that question. We are mindful of the need to try
19 to assess the impact on the blood supply of any
20 potential change to our donor exclusion policy and,
21 indeed, we have already had dialogue with major blood
22 organizations on both the feasibility and scope of
23 surveys that could establish the impact of any
24 candidate deferral policy related to Canadian exposure
25 on the U.S. blood supply.

1 And more broadly speaking also, we are
2 thinking about similar questions as they might pertain
3 to say exposure in Japan or other countries that have
4 had case reports of BSE in cattle. So that enterprise
5 is recognized and is ongoing.
6 BOARD MEMBER WOLFE: So you are going to
7 be collecting data on what this impact would be?
8 DR. EPSTEIN: Well, blood organizations
9 have been asked --
10 BOARD MEMBER WOLFE: Right.
11 DR. EPSTEIN: -- if they would collect
12 such data, and we have had preliminary statements of
13 agreement.
14 BOARD MEMBER WOLFE: Okay. Thank you.
15 CHAIR PRIOLA: Any other questions for Dr.
16 Epstein? Okay. Thank you very much.
17 DR. EPSTEIN: Thank you.
18 CHAIR PRIOLA: Our next speaker will be
19 Dr. Robert Hills from Health Canada Ottawa who will
20 discuss the review of Bovine Spongiform
21 Encephalopathies in Canada.
22 DR. HILLS: All right. First, thanks very
23 much for inviting me to give you a little update of
24 what the situation is in Canada right now with respect
25 to BSE. I will just wait for the slides to come up.

1 There is a fair bit of information on the slides, so
2 what I will try to do is go through it relatively
3 quickly. All right. Thanks a lot.
4 First of all, I thought what I would do is
5 give you a little bit of background to what Canada has
6 been doing with respect to BSE before we found a case
7 in May of this year. First of all, there was a
8 prohibition of the importation of products assessed to
9 have a high-risk of introducing BSE in Canada. There
10 was importation of meat and meat products only from
11 countries that Canada recognized as being BSE-free.
12 In 1990, there was a designation of BSE as
13 being a reportable disease in Canada, and any suspect
14 case of BSE would be reported to a federal
15 veterinarian. In 1992, there was the creation of the
16 National BSE Surveillance Program. In 1997, the same
17 year as the U.S. did, as well, there was the
18 implementation of the feed ban of feeding rendered
19 protein products from ruminant animals to other
20 ruminants. In the year 2001, there was the creation
21 of the Canadian Cattle Identification Program for
22 Cattle and Bison making it possible to trace
23 individual animal movements from the herd of origin to
24 the slaughter.
25 Next slide, please. This is just a quick

1 pictorial of sort of how Canada has approached it.
2 Canada has adhered to the OIE guidelines on TSE risk
3 management. Up until our finding of the case, we were
4 considered to be provisionally free, and we have also
5 done a risk assessment that was completed in December
6 of 2002 with respect to Bovine BSE cattle in Canada,
7 and in that risk assessment, we actually determined
8 that the likelihood of finding BSE in Canada would be
9 remote. That has changed, but still remote.
10 Next slide, please. Before we go on, what
11 I would like to do though is just bring you back a
12 little bit in time, because we did have a case
13 previously. In 1993, we did diagnose a case of BSE in
14 a beef cow that was imported from the UK in 1987. The
15 exposure of this animal to BSE occurred prior to its
16 arrival to Canada. The index herd and all the UK
17 animal imports were destroyed, at the time, and it was
18 subsequently determined that the UK herd, which was a
19 source cow for this particular animal, did have other
20 infected animals, as well.
21 Next slide, please. This graph here is,
22 again, a pictorial showing the importation of animals
23 into Canada, particularly, and we're it the North
24 American Disposition of Imported UK Cohort Members
25 prior to the index case discovery in 1993. So there

1 was importation of animals prior to our taking action
2 in 1993 to eliminate those animals.
3 Next slide, please. So getting on to our
4 first indigenous case. January 31, 2003, a 6 to 8
5 year-old downer beef cow from northern Alberta went to
6 slaughter to a provincially licensed meat facility.
7 Alberta Agricultural Food and Rural Development meat
8 inspector condemns the carcass as being unfit for
9 human consumption.
10 At that time, the head was collected and
11 submitted as part of our National Surveillance
12 Program, the Federal Provincial Surveillance Program
13 for BSE. And the carcass, at that time, because it
14 was condemned, was sent to inedible rendering.
15 Next slide, please. On May 16th, the
16 testing was completed with a tentative diagnosis of
17 BSE by the Alberta Ministry of Agriculture. The
18 sample was then sent immediately to Canadian Food
19 Inspection Agency's National Center for Foreign
20 Disease in Winnipeg, Manitoba where they also
21 confirmed BSE, and then the sample was subsequently
22 sent to the Veterinary Laboratory Agency in Weybridge,
23 England, which is the OIE Reference Center for BSE.
24 And on May 20th, they actually confirmed our diagnosis
25 of it being an actual case of BSE. Immediately upon

1 notification, we notified the OIE, in fact, that we
2 did have a case of BSE.
3 Next slide, please. So what did we do
4 from there? So we had a start in epidemiological
5 investigation. We basically broke it down into three
6 phases. The first phase, we're calling that the case
7 itself, which we'll call the animal trace back, its
8 immediate management, which we'll call the animal
9 trace forward, and the most probably origins, which is
10 where did the animal get the exposure from?
11 Next slide, please. This is a well used
12 graph. It is done in colors for a particular reason.
13 The red is the case herd where the index animal was.
14 The blue line is considered the primary line of
15 inquiry where we think the source animal came from,
16 which is in Saskatchewan. The yellow line is
17 considered the secondary line of inquiry. That was an
18 Alberta line, and the green one in the middle is, in
19 fact, that we did discover that there was some
20 commingling with another herd. So those are the
21 areas, which we were tracing out as part of this
22 investigation.
23 Next slide, please. As I said earlier,
24 the index case was a 6 to 8 year-old Angus. It was a
25 member of a herd that was recently established within

1 a two year period between 2001 and 2002, and the
2 animals that made up that herd were from two farms.
3 What we believe initially from the age of the animal
4 was that the expression of the clinical BSE at this
5 age offers the first epidemiological insight, which
6 would probably mean it was a low level BSE exposure
7 given the age of the animal.
8 As I mentioned earlier in a previous
9 slide, the Saskatchewan blue line of inquiry was the
10 most probable avenue for which the positive animal
11 moved to the Alberta farm. That particular line of
12 inquiry, the animals were culled and depopulated and
13 tested, and all tests were negative by Prionics
14 Western Blot and immunohistochemistry.
15 Next slide, please. At the same time as
16 we were culling and depopulating and testing, we were
17 also trying to confirm through DNA testing the origin
18 of the particular index animal. Unfortunately, the
19 DNA testing did not come back with a clear definitive
20 result, and as a result, we needed to then move down
21 the second line of inquiry.
22 So we proceeded with the depopulation and
23 testing of animals in the Alberta line of inquiry,
24 which was that yellow line in the previous pictorial
25 that I showed you. We culled those animals and tested

1 those animals and all tests came back negative again
2 from Western Blot and immunohistochemistry. Even
3 though we didn't have a confirmed definitive answer
4 for the DNA, it is still a probably line of inquiry,
5 and most probable one, is the Saskatchewan blue line
6 for the introduction of the animal to this farm.
7 Next slide, please. The next phase, which
8 was the Animal Trace Forward Investigation, was to
9 determine what would happen with the animals that left
10 the farm. So there was movement. We looked for the
11 movement of the cattle from the index herd. We looked
12 at, as I mentioned earlier there was a green box,
13 where there was some commingling. We traced out those
14 animals. We culled them. We depopulated them. We
15 tested them. We found that they were all negative by
16 Western Blot and immunohistochemistry.
17 Next slide, please. So to summarize, the
18 Trace Forward and Trace Back Investigations, we had 15
19 premises that were quarantined, an additional 25 herds
20 were scrutinized and the tracing-out of single animals
21 or cohorts from the Saskatchewan line of inquiry.
22 The trace out also included the
23 identification and notification of the export of five
24 animals to the United States, which you all should be
25 aware of, we did let you know as soon as we found that

1 out. And in all, we had a culling of more than 2,700
2 animals, 2,000 of which were 24 months of age and
3 older, and all, as I mentioned earlier, have been
4 found negative by Prionics Western Blot and
5 immunohistochemistry.
6 Next slide, please. This is just a
7 pictorial or a graphic of the disposition of the
8 carcass of the particular BSE index case. It shows
9 the yellow line, which shows the line of investigation
10 with respect to the use of the products for laboratory
11 testing. We have the lighter blue line, which shows
12 what happened with the processing of the hide. And
13 then, again, we have the mauve or the purple, which is
14 moving the carcass to inedible rendering and what
15 happened to it from there. And as you can see, it did
16 get rendered into some meat and bone meal.
17 Next slide, please. So we then looked at
18 the Feed Investigation. Since the index cow was
19 condemned unfit for human consumption, its carcass was
20 sent to an inedible rendering. And I would want to
21 reemphasize because it was sent to inedible rendering,
22 there was no part of the animal that actually went
23 into the human food chain.
24 Next slide, please. The carcass of the
25 index as I showed you in the previous pictorial, the

1 carcass of the index case was traced via Canadian Food
2 Inspection Agency from the abattoir, the renderer, the
3 feed mill, the producer continuum to its direct
4 allocation into pet food. And in the pet food case,
5 we did find that actually there was some pet food that
6 actually was exported to the U.S. to which we notified
7 the U.S. when we found that out, and there was pet
8 food in Canada, as well. And there was the production
9 of meat and bone meal.
10 What is important to take out of this
11 though is the visit to the renderer and the feed mills
12 confirmed adherence to our feed ban or meat and bone
13 meal feed ban legislation on the product receipt,
14 segregation, labeling and distribution. So there was
15 no breach in compliance, at that point, at the
16 renderer. So it was not labeled to be fed back to
17 ruminants.
18 Next slide, please. Further investigation
19 was the trace out of the feed to individual farms, and
20 we did find that three additional farms were
21 quarantined when the investigation could not preclude
22 exposure of 63 head of cattle to the feed destined for
23 poultry feed. In that case, it was evidenced that the
24 farm itself had allowed poultry feed to be fed to
25 ruminants. The animals were culled and tested by

1 Prionics Western Blot and immunohistochemistry and,
2 again, all those animals came back negative.
3 Next slide, please. This is just a
4 pictorial, again, of what I was describing before from
5 the inedible material from the index case going to the
6 renderer. It went up to pet food. It went into
7 poultry and some pet food, and there was the feed
8 mills that we traced out afterwards. So this is sort
9 of managing the risk of the disposition of the
10 material from the index animal.
11 Next slide, please. There were other
12 considerations that we wanted to take into account as
13 we proceeded in with the exposure investigation. We
14 did look at maternal transmission. We looked at
15 contaminated meat and bone meal used in feed products,
16 particularly early risk factors, any UK imports
17 slaughtered prior to 1993 or other European imports.
18 It was figured into our investigation.
19 We looked at TSEs resident in other
20 animals, CWD and scrapie as examples, and we did look
21 at the possibility of it being a spontaneous case.
22 Our investigation right now is at the point now, we
23 are looking at feed products that are considered the
24 most probable root of exposure.
25 Next slide, please. Again, this is just

1 a graphic again to illustrate the hypothetical foreign
2 domestic exposures of the index case, and it's just
3 groups of, you know, what the possibilities might be
4 for the exposure of this particular case.
5 Next slide, please. What we did find out
6 in the investigation is there was two potential meat
7 and bone meal epidemiological exposure roots that were
8 identified. The first was a feed concentrate and the
9 second was a high energy feed block. Both have
10 incorporated meat and bone meal, at some point in
11 time. The investigation did find though that the feed
12 mill records and compounding formulae confirmed that
13 the meat and bone meal incorporated in both of these
14 products was curtailed in 1997 upon implementation of
15 the meat and bone meal feed ban.
16 Next slide, please. So what can we
17 conclude? What we can conclude so far is that
18 discovery of BSE in Canada proves that the active
19 surveillance and the diagnostic programs were working,
20 because we did find the case. Epidemiological
21 evidence supports the probability that BSE in this
22 case animal was associated to exposure to infected
23 material through the feeding system, at some point,
24 early in the animal's life.
25 Next slide, please. What we felt that we

1 needed to do was to ensure that what we were doing was
2 accepted and would be recognized, so it was decided
3 that what we would do is convene an expert panel to
4 actually go over our procedures and how we did it and
5 what we were doing and what actions we were going to
6 be taking, and get their recommendations back to us.
7 That particular panel comprised of Ullie
8 Kihm from Switzerland, Will Hueston from the USA,
9 Dagmar Heim from Switzerland, and we did have contact
10 with Stuart MacDiarmid from New Zealand, as well. The
11 first three met on June 7th to 9th and met with the
12 members of the Canadian Food Inspection Agency and
13 Health Canada to which the team was provided with an
14 overview of the epidemiological investigation. All
15 actions taken to date and the scope of the options and
16 the measures being considered to adjust domestic
17 policies.
18 Subsequently to that meeting, the team
19 went back and did actually do a report, and what the
20 panel did find was that the -- they found that the
21 risk management measures put in place in Canada
22 achieved the desired outcome. The surveillance did
23 detect the case with BSE. The animal did not enter
24 the food chain and the measures in place have reduced
25 the spread and amplification of BSE in Canada.

1 Next slide, please. They did come back
2 with some specific recommendations, however, for us to
3 strengthen our current situation. They did say that
4 there should be a prohibition on Specified Risk
5 Materials in human food and animal feed, including
6 advanced recovery meat products, tighter controls on
7 non-ruminant feed, enhanced audit and compliance,
8 strengthening the existing cattle identification
9 tracking and tracing systems that are existing in
10 Canada, enhanced disease testing and surveillance by
11 increasing the coverage of fallen and dead stock,
12 downer and diseased animals, and to work at efforts to
13 improve the awareness among producers, veterinarians
14 and the general public with respect to BSE.
15 Next slide, please. So what will Canada
16 do? Well, the government of Canada will be responding
17 to the recommendations of the International Team.
18 We'll respond through our consultation process with
19 our provinces or territories, the Canadian industry,
20 our U.S. counterparts and other trading partners, and
21 there will be a new policy measure for Specified Risk
22 Materials as being the first step.
23 Next slide, please. I felt before we sort
24 of should go a little bit further, I would just give
25 you a little bit of background about -- because I'm

1 going to be talking about Specific Risk Materials Ban
2 right now, which is the first step, that in Canada, 95
3 percent of the slaughters is in federally registered
4 establishments and the majority of those animals that
5 are slaughtered are between the age of 18 and 24
6 months.
7 5 percent of the slaughter is in
8 provincial abattoirs and the majority of those being
9 over 30 months of age. Only animals slaughtered in
10 registered establishments can be exported. The
11 provincial slaughtered animals can only be traded
12 within provinces and sold within provinces. If they
13 are to leave provinces or to leave the country, they
14 have to be at a registered establishment. Removing
15 SRMs at the point of slaughter and disposing of them,
16 we estimate removes about 99 percent of the human
17 exposure to potentially infected material.
18 Next slide, please. The immediate
19 objective of the SRM policy is to establish a
20 requirement that the SRMs be removed at the time of
21 slaughter, and that they be removed from human use,
22 human food and human use. The new policy will define
23 Specified Risk Materials and require removal, as I
24 mentioned earlier, at slaughter.
25 The list that I have right here are some

1 of the things that we have been considering as being
2 the most probable. They will likely include the
3 brain, spinal cord, dorsal root ganglia, eyes,
4 tonsils, skull and distal ileum.
5 Next slide, please. Following our first
6 step, as was recommended in the expert panel report,
7 there will be other measures that will be taken.
8 There will be areas that will be looked at with
9 restrictions on animal feed and process and protect
10 human and animal health, that should be, expanded
11 surveillance, as was mentioned earlier, expanded food
12 safety plans, comprehensive tracking and tracing
13 systems and national standards and approaches will be
14 implemented in Canada.
15 Next slide, please. And that concludes a
16 very quick overview of what we did. Hopefully, it did
17 give you an idea of the scope in which we reacted and
18 what we looked at. I have listed here a number of
19 different sites that you can look at for updates.
20 We're trying to be as open and as transparent about
21 our investigation or actions as we possibly can, and
22 I would encourage you to go to these sites and go to
23 this to get the most up to date information. That's
24 it.
25 CHAIR PRIOLA: All right. Thank you, Dr.

1 Hills. Dr. Wolfe?
2 BOARD MEMBER WOLFE: This morning, we sent
3 a letter to the Secretary of Agriculture, Veneman,
4 strongly urging them not to lift the ban on meat
5 coming from Canada to this country, and one of the
6 questions we have was, and I will just read you three
7 sentences, because it's really the form of the
8 questions.
9 Public information regarding the
10 enforcement of the Canadian Feed Ban, and we know it
11 went into effect in '97, but we also know the data
12 from the United States show very spotty and uneven
13 enforcement, particularly, the first few years of the
14 ban, which is very similar to the U.S. ban and was
15 enacted about the same time. It's available, it's
16 data unenforcement. It's not on the website of the
17 Canadian Food Inspection Agency and a telephone call
18 to the agency requesting these data has not produced
19 any information. Most tellingly, the report from the
20 team of international experts, which is, I assume, the
21 one you just referred to.
22 DR. HILLS: Yes.
23 BOARD MEMBER WOLFE: That investigated the
24 Canadian government's response to the outbreak makes
25 no mention of compliance with the feed ban. It

1 mentions the feed ban, of course, but data
2 incompliance.
3 DR. HILLS: Yes.
4 BOARD MEMBER WOLFE: It is simply
5 impossible to assess the wisdom of lifting the ban you
6 wisely put in place, you, Secretary Veneman, in this
7 case, on an emergency basis without these data.
8 So my question to you is what is your
9 knowledge? I thought your presentation was excellent.
10 What is your knowledge of looking backward how
11 effective the enforcement of the feed ban has been
12 from 1997 when it was imposed to now?
13 DR. HILLS: Unfortunately, I don't have
14 the history to go back in time from '97 backwards or
15 forwards. I know it has come up in our discussions
16 numerous times, being able to put some sort of
17 quantifiable number to it and to try to do that. I
18 have not yet seen that myself. We are trying to
19 determine that now, because we have had
20 investigations. We have looked at it. We have found
21 that our plants themselves have been in compliance.
22 As I noted in our Feed Investigation, we
23 did find though that there was a possibility that if
24 a farm was coproducing, that there was a possibility
25 of cross-contamination, if you want to call it that,

1 and those are things that we're trying to address now
2 to improve.
3 BOARD MEMBER WOLFE: Yes, I mean, needless
4 to say, it's the essential issue, because you have
5 admitted that that's the most likely place that the
6 cow that got infected got infected from, and given --
7 DR. HILLS: Well, no, that's not quite
8 what I said.
9 BOARD MEMBER WOLFE: Well, I think it's
10 all on your slides, for the most part.
11 DR. HILLS: No, I think what I said was we
12 found that there were three slides as part of the
13 investigation from the index case that actually found
14 that there were three farms in B.C. that actually were
15 not in compliance, because they inadvertently had fed
16 or that we couldn't definitively tell whether or not
17 the feed that was destined for poultry did not end up
18 having inadvertently been fed to ruminants. What I
19 said was that our most likely possibility would be --
20 BOARD MEMBER WOLFE: The feed.
21 DR. HILLS: -- exposure before the feed
22 ban.
23 BOARD MEMBER WOLFE: For that particular
24 cow.
25 DR. HILLS: Yes.

1 BOARD MEMBER WOLFE: But, you know, again,
2 are there going to be some data on enforcement? I
3 mean, I assume that once it went into effect, there
4 was some kind of government effort.
5 DR. HILLS: Yes.
6 BOARD MEMBER WOLFE: To check on
7 enforcement.
8 DR. HILLS: Yes.
9 BOARD MEMBER WOLFE: When can we expect to
10 see those data?
11 DR. HILLS: I can't give you a date on
12 that. I can certainly find out for you, but I cannot
13 give you that, but I am not aware of what date they
14 are going to be able to make that information
15 available.
16 BOARD MEMBER WOLFE: Okay. Thank you
17 again, very good presentation.
18 CHAIR PRIOLA: Dr. Johnson?
19 BOARD MEMBER JOHNSON: Yes. Dr. Hills, a
20 question that was brought up early on was the possible
21 U.S. origin of that cow, that it might be a North
22 Dakota or Montana cow, and it may have been our feed
23 ban was the problem. Is there any further data on
24 that original origin of it, and has the U.S. origin
25 been ruled out?

1 DR. HILLS: The data we have right now
2 suggests that the line of inquiry was the source was
3 the Saskatchewan farm right now. We have no
4 definitive evidence that would say that it was an
5 animal that was imported from the U.S.
6 CHAIR PRIOLA: Dr. Gambetti?
7 BOARD MEMBER GAMBETTI: Can you describe
8 the procedure that Health Canada uses to diagnose this
9 particular animal and suspected animal in general?
10 You listed Prionics Western Blot and the
11 immunohistochemistry. Is that done in more than one
12 area and in that particular animal that turned out to
13 be positive, were both positive? Can you, in other
14 words, amplify a little bit on how the animal or
15 another animal are studied in Canada?
16 DR. HILLS: If I understood your question
17 correctly, Canada has a national TSE laboratory
18 network. The gold standard, the immunohistochemistry
19 test, is a test that is used, was used in all these
20 laboratories, and so there was, as I mentioned
21 earlier, the National Surveillance Program.
22 The Prionics test for Western Blot was
23 brought in and we were evaluating it, at the time, but
24 it was brought in for use mainly because we had so
25 many animals to do, at the time, that we needed to

1 find some mechanism by which we could up the volumes,
2 and at the same time, we feel that it was a mechanism
3 by which we could do validation testing on the
4 Prionics test itself.
5 So in doing that, the work was done in the
6 Alberta and Winnipeg labs for the Prionics test, but
7 we're in the process now of looking at and getting
8 that test now distributed across the TSE laboratory
9 network.
10 BOARD MEMBER GAMBETTI: How many tissue
11 samples or brain area were examined, only one, the
12 lower medulla or more than one and were all of them,
13 if there were more than one, were they all positive?
14 DR. HILLS: I believe there was more than
15 one and yes, they were all positive, but I can't give
16 you the exact number.
17 CHAIR PRIOLA: Dr. Bracey?
18 BOARD MEMBER BRACEY: Perhaps along that
19 line, I guess a question that comes up is the issue of
20 with any test, there is always the chance of having a
21 false positive the more times you do an assay. How
22 are you all, in essence, getting at that and is there
23 a plan to actually look at infectivity in some of
24 these animals or do you feel, in essence, confident
25 enough with the assay system in terms of eliminating

1 that rare false positive?
2 DR. HILLS: Well, that was one of our
3 concerns, was to go to tests other than the
4 immunohistochemistry analysis, but we felt that the
5 information that we have generated now based on the
6 culling exercise that we have gone through with the
7 animals that we have right now, because each one of
8 those animals was testing in parallel with the gold
9 standard test, that we felt that we're starting to now
10 get the numbers that would indicate whether or not the
11 test is, in fact, what the manufacturer suggests,
12 which is 100 percent no false negatives. So we are
13 generating the information now, and that is the only
14 way that we can do it.
15 BOARD MEMBER BRACEY: What about the issue
16 of false positives though?
17 DR. HILLS: Well, in doing the animals
18 that we're doing now, we have found no false
19 positives, but that, as I said, was only 2,700
20 animals. That is what we have done. That is the
21 claim of the Prionics, I believe, is what they are
22 suggesting is it is being 100 percent accurate.
23 I did mention that the animals that we
24 were talking about were -- we were targeting 24 months
25 and older animals, because we still believe that there

1 is some possibility that the test will not work
2 sufficiently well for animals below that age, and so
3 the testing system itself is probably a little
4 questionable for younger animals.
5 CHAIR PRIOLA: Dr. Nelson?
6 DR. NELSON: You mentioned that there were
7 2,700, I think, animals that were tested and found not
8 to be -- not found any positives, but how many were of
9 the similar age to this animal? In other words, the
10 infection in this animal could have occurred six,
11 seven years ago and not shown up if the animals
12 examined where younger.
13 DR. HILLS: Yes, that's a very good
14 question. That's why when we were looking at the
15 culling and the depopulating, we were looking at the
16 specific herds, so we were getting an age
17 distribution. I can't give you the exact number of
18 animals that were there, but because we were targeting
19 the animals older than 30 months, we would then take
20 into account some of those animals. And some of those
21 herds on the Saskatchewan side were breeding animals,
22 so many of them were older. I just can't give you the
23 exact number.
24 CHAIR PRIOLA: Dr. Taylor, did you have a
25 comment?

1 DR. TAYLOR: David Taylor from Edinburgh.
2 You mentioned how you concluded that because clinical
3 disease emerged somewhere between when the animal was
4 somewhere between 6 and 8 years-old, that this may be
5 reasonably construed as evidence of low level
6 challenge. Now, certainly, it is true in the UK that
7 incubation period as we have taken to broadly equate
8 with age, because meat and bone meal was usually and
9 often only fed in calf food.
10 But if the animal, in fact, received meat
11 and bone meal A for the first time or subsequently on
12 several occasions after it was born, you can't really
13 pin down the incubation period. So it could still be
14 a high level dose if it got its meat and bone meal at
15 a later stage.
16 DR. HILLS: Yes, you are correct. I have
17 no trouble with what you're saying, but I will go back
18 to our feed ban that we have in place right now. The
19 fact that the feeding of animals back and forth, the
20 feeding of ruminant material back to ruminants is
21 prohibited in Canada, so the likelihood of that would
22 be, in our estimation, remote, not nil, but it would
23 be remote. So yes, so that's what we're saying is we
24 do think it's preceding the feed ban, so that would
25 make it then '95, '96, somewhere around in there, and

1 it is a possibility, yes, at that time.
2 CHAIR PRIOLA: Dr. Bailar? I'm sorry, Dr.
3 Bailar, excuse me.
4 BOARD MEMBER BAILAR: You mentioned the
5 Canadian system for identification, tracking and
6 tracing of animals. How much help was that to you in
7 your investigation?
8 DR. HILLS: It was significantly helpful
9 for us. Unfortunately, because we instituted it in
10 the year 2001, it really only was successful for
11 animals that were within that age group. Even though
12 all animals are tagged for movement now, what we can't
13 do is really definitively say, for example, the age of
14 the animal, where the entire history of the animal
15 was, but for the younger animals, yes, we can do that.
16 So after 2001, we can certainly trace it.
17 BOARD MEMBER BAILAR: Can anyone tell us
18 about the present status of moves to have such a
19 system in the U.S.? I'm sorry Dr. Ferguson isn't here
20 now. I'm concerned, of course, about the possibility
21 that there might be a single case here sometime.
22 CHAIR PRIOLA: Yes, and I'm not sure
23 anyone here can answer that. That is sort of a USDA
24 issue, not an FDA one, I think. We're about to
25 proceed to the open public hearing portion. Do you

1 gentlemen have a couple of quick questions? You have
2 been standing very patiently. Do you have a couple of
3 quick questions for the speaker?
4 MR. HAFFENDEN: Yes, Paul Haffenden from
5 TerraCell. I would just like you to comment. Several
6 years ago, the European Scientific Steering Committee
7 assessed Canada and the U.S. as category 2 countries,
8 equivalent risk, given the -- maybe you could comment
9 on the movement, high incidence of movement of animals
10 between the two countries in both directions, high
11 incidence of movement of animal feed products between
12 the two countries in both directions, and then any
13 comment on how you think that might affect the
14 adjustment and category risk now with this case in
15 Canada?
16 DR. HILLS: I don't think I can discuss
17 anything about how that is going to affect the
18 categorization. I think that is something that
19 somebody else will determine, not me. But what I can
20 say is that given the trade between our two countries,
21 there is movement of both animals and feed across the
22 border.
23 CHAIR PRIOLA: If it's a very quick
24 question.
25 MR. BROOKLANG: Yes, Nelson Brooklang,

1 Ortech International, New York. You made a
2 distinction between federally registered and
3 provincially registered abattoirs and the age of
4 cattle that are processed in those, and the fact that
5 provincial cattle don't get exported. I wanted to ask
6 whether blood byproducts used in the biotech industry,
7 what I am from, like Bovine Serum Albumin transferred,
8 purified from bovine blood could be collected from
9 provincial abattoirs in Canada and sold in the U.S.?
10 DR. HILLS: Good question. My
11 recollection is that the material itself is not. From
12 the provincial licensed establishments, the provincial
13 government looks after that, and I do not believe it
14 then goes to the federally registered renderers, but
15 I would have to reverify that. I'm not 100 percent
16 sure.
17 CHAIR PRIOLA: Okay. Thank you very much
18 for your presentation. I will move on to the open
19 public hearing portion.
20 SECRETARY FREAS: In response to our
21 Federal Register announcement, I have received two
22 requests to speak at today's open public hearing for
23 this afternoon, and the first one is Mr. Wayne Vaz.
24 Would you, please, come to the microphone and make
25 your presentation?

1 MR. VAZ: Good afternoon. My name is
2 Wayne Vaz. I am representing Serologicals
3 Corporation. We are a leading supplier of animal-
4 based products of the global health care industry. We
5 are based in Atlanta, Georgia with more than 800
6 employees worldwide. We greatly appreciate the
7 opportunity to be here today to talk about the TSE
8 safety of our bovine products and their critical
9 importance in global health care.
10 Next, please. Our goal is to raise the
11 level of awareness regarding the pervasive use of
12 bovine products in the production of life-saving drugs
13 and other essential health care products. We want to
14 present the facts according to high safety and qualify
15 of Serologicals' bovine-based products, and we would
16 like to work with the TSE Advisory Committee and
17 regulators to further develop industry guidelines to
18 assure the continued availability of bovine products.
19 Next, please. Serologicals is a global
20 provider of biological products and enabling
21 technologies, which are essential for the research,
22 development and manufacturing of biologically-based
23 life science products. Some examples of our products
24 include antibodies, cell culture supplements, such as
25 bovine albumin and other products for diagnostic and

1 research.

2 Next, please. This is a listing of our

3 bovine-based products. We're focusing on this,

4 because these are the products that are believed to

5 offer a theoretical TSE risk. At present, we have two

6 manufacturing facilities, one in Toronto, Canada, the

7 other in Kankakee, Illinois. We have a third facility

8 under construction in Lawrence, Kansas.

9 Next, please. Our bovine-based products

10 are used in the development and production of life-

11 saving FDA-approved drugs, FDA licensed diagnostics,

12 medical devices and animal vaccines. Our bovine-based

13 products are used in the development and production of

14 FDA approved biologics for treatment of cancer,

15 arthritis, Crohn's Disease, psoriasis, blood clotting

16 disorders, spondylitis, RSV and at least one

17 genetically predisposed orphan disease.

18 In the diagnostic area, our bovine

19 products are used in the screening of U.S. blood for

20 key viruses, such as HIV and HCV, for screening of

21 cancer markers and in serological testing as a

22 potentiator of blood typing prior to transfusions. In

23 medical devices, our bovine products are used in the

24 production of a medical device that is used during

25 surgery, and in animal vaccine, our products are used

1 for the cultivation of Leptospira, which is used to
2 produce animal vaccines for the treatment of
3 Leptospirosis, which is a worldwide problem in
4 livestock. Also, these bovine products are used
5 pervasively in life science research as reagents in
6 the lab for protein assays and other lab assays like
7 chromatography and electrophoresis.
8 Next, please. So in April of 2000, we
9 received an update, which was issued to manufacturers
10 of biological products from Kathryn Zoon, the former
11 director of CBER, that essentially says avoid using
12 ruminant origin products derived from BSE-affected
13 countries in the production of FDA-regulated products
14 that are intended for humans.
15 Make sure you identify all the ruminant
16 materials used in production of the regulated
17 products, and document the country of origin, and make
18 sure you maintain traceability records for each lot.
19 Of course, the purpose of this guidance is to minimize
20 the TSE threat to the public.
21 Next, please. So this creates some
22 regulatory uncertainty regarding the products under
23 development today that are made using bovine
24 ingredients. Also, there is a risk of current
25 production of approved drugs, which use bovine

1 ingredients. This may lead to a possible interruption
2 to the supply of these biotech drugs if BSE occurs in
3 the U.S. Bovine-based products provide unparalleled
4 performance. There has been a few attempts to replace
5 these products in cell culture, but they typically
6 result in lower productivity and higher costs.
7 Next, please. I would like to switch
8 gears for a minute and talk about the prion
9 infectivity clearance studies that Serologicals has
10 conducted. We scaled down our manufacturing processes
11 and we used a hamster-adapted strain of scrapie agent
12 as a model to emulate the BSE. Like many
13 presentations before, we used a 263K agent. We spiked
14 known titres of infectivity prior to key process
15 steps, and using serum tenfold dilutions we titrated
16 the infectivity downstream to measure the ability of
17 the intervening steps to reduce infectivity, looking
18 at that in-vivo using hamsters and looking at the
19 clinical signs, abnormal gait, tremors, ataxia or
20 incoordination, also looking at a histopathological
21 examination of the brain tissue to confirm the
22 clinical diagnosis, and the characteristic protease
23 resistance of the transformed prions.
24 The conclusion of these studies, if you
25 look at our Bovine Serum Albumin product line, our HS

1 product line, looking at four process steps achieving
2 a total clearance of 16 log10, Bovine Aprotinin, a
3 total of 17 logs and EX-CYTE completing one
4 manufacturing step to date, achieving 3.7 log10.
5 Next, please. So we feel that these prion
6 clearance studies offer some objective evidence that
7 these products are very safe from a TSE risk. In
8 summary, the high safety and quality of our bovine-
9 based products are summarized by the following.
10 One, many are manufactured from bovine
11 blood, which is recognized as being low-risk of TSE
12 infectivity, according to the World Health
13 Organization and the EC. Moreover, Serologicals use
14 either plasma or serum for added safety. One of the
15 theories is that it is believed that prions may reside
16 in the cellular fraction of blood, for example,
17 leucocytes. We only use bovines that are less than 30
18 months of age, and they are typically less than 20
19 months of age.
20 According to the DEFRA statistics in Great
21 Britain, no BSE reported in cattle that is less than
22 20 months. It is uncommon for it to happen in less
23 than 30 months. We use only USDA-approved raw
24 materials collected in USDA-licensed establishments.
25 All these products are manufactured within an ISO 9002

1 registered GMP environment.
2 We have completed and published prion and
3 viral clearance studies, and this compounded with the
4 similar clearance studies that our customers have
5 completed that are producing these biologics, we also
6 maintain EDQM certificates of suitability, which again
7 is an assessment of low TSE risk. We have a proven
8 track record of safety in global health care.
9 Next, please. So this is an example of
10 one of the viral clearance studies that we have
11 completed on our bovine product line. Due to time
12 constraints, I won't get into this other than to say
13 that we have demonstrated more that 6 log10 of bovine
14 viruses.
15 Next, please. So in summary, one, bovine-
16 based products are critical to the production of life-
17 saving health care products. Secondly, manufacturers
18 of FDA-regulated products cannot replace bovine
19 ingredients quickly, easily or economically. The high
20 safety and quality of Serologicals' products is
21 supported by the low TSE risk raw materials that we
22 use, the controlled production and the research
23 studies that we have conducted that demonstrates
24 robust virus and prion clearance ability of the
25 manufacturing process, and our track record of safety

1 and success. We're pleased to work with the TSE
2 Advisory Committee to further develop the TSE risk
3 guidelines covering these important products to permit
4 their continued use.
5 Next, please. Some considerations. In
6 addition to using low TSE risk raw materials, why not
7 recognize the value of prion clearance studies and
8 let's establish minimum acceptance criteria. Let's
9 have suppliers perform prion clearance studies to
10 provide objective evidence supporting the product
11 safety. Also, why not consider prohibiting the
12 sourcing from countries with a high incidence of BSE,
13 rather than just one or two cases?
14 And finally, when it comes to setting
15 policy, we would request that the FDA and the USDA
16 carefully weigh the impact to the end consumers, i.e.,
17 the patients, producers of biomedical products, which
18 are our customers and supply chain producers like
19 Serologicals.
20 Next, please. Finally, we would like to
21 leave you with two contacts at Serologicals
22 Corporation. If any of you wish to discuss this
23 further, we would be happy to do that. Our email
24 addresses are listed. Thank you very much.
25 SECRETARY FREAS: Thank you for your

1 comments. Our next speaker for this open public
2 presentation is Dr. Merlyn Sayers.
3 DR. SAYERS: Excuse me. Thanks for this
4 opportunity to talk to you. See if you can rustle up
5 my first illustration. It's a brave blood bank of the
6 talks in the immediate shadow of the regulators, so I
7 am indebted to Dr. Hills and to Mr. Vaz for giving me
8 some narrative separation from Dr. Epstein.
9 No, let's have the earlier slide, please.
10 I'm speaking to you as the CEO of Carter BloodCare,
11 and that's the community independent blood program
12 that meets the transfusion needs of something like 150
13 hospitals in the Dallas, Fort Worth area. I am also
14 speaking to you as a former chairman of the Blood
15 Products Advisory Committee and as a consultant to
16 this group, and I only make those two comments to
17 emphasize how keenly I appreciate the challenges that
18 the regulators confront and also advisory groups like
19 yours have to confront, as well.
20 By way of a preface, let me have the first
21 illustration. Something like 40,000 Americans donate
22 every day and their health history, their screening
23 for markers of diseases that are potentially
24 transmissible by transfusion, their subsequent
25 counseling if that counseling is indicated, these

1 elements constitute what is perhaps the largest public
2 health exercise in the country and might even be the
3 largest public health exercise in the world.
4 Now, bear in mind that those 40,000
5 individuals that donate originally were some 50,000
6 individuals, close to 50,000. Of course, many get
7 deferred during the history and examination even
8 before any serological testing is done on those folk.
9 So what happens at a local level?
10 At Carter BloodCare, at our blood program,
11 last year we registered something like 270,000
12 individuals, 40,000 were deferred and they were
13 deferred either permanently or temporarily, as I say,
14 even before testing. The majority of these deferrals
15 certainly are temporary deferrals, and they are
16 attributable to medications that those individuals
17 might have been on. They might have a low hematocrit.
18 They might have traveled to a malaria area.
19 But those temporarily deferred individuals
20 are of particular interest to us as blood bankers,
21 because potentially those individuals are individuals
22 that we could get back to continue their donation to
23 the community's needs. We have been considering what
24 has happened to temporarily deferred blood donors for
25 a long period of time.

1 May I have the next illustration, please?
2 What is their subsequent conduct? We looked to 500
3 temporarily deferred donors and followed them for two
4 years, and you can see from this illustration that
5 58.5 percent returned to donate successfully. 8
6 percent returned only to be deferred again, but 33.5
7 percent of that original starting temporarily deferred
8 group did not return.
9 So for one third of temporarily deferred
10 donors, that temporary deferral is so discouraging an
11 experience that those individuals resist all our
12 entreaties for them to come back and donate again.
13 Now, the likelihood of deferral is obviously
14 proportional to the amount of scrutiny that these
15 individuals are subjected to.
16 So let's have the next illustration. And
17 certainly, the amount of scrutiny that donors are
18 being subjected to has increased dramatically. You
19 can see the number of questions that donors were asked
20 in 1988 and the number of questions donors are asked
21 in 2003. For those of you that are donors, the donor
22 history questionnaire does not list 160 separate
23 questions. It's probably closer to 40, but each
24 question has become so complex. There are multiple
25 questions. There are questions within questions.

1 There are nested questions. So what we now want are
2 160 pieces of information from donors.
3 So where do these increasing scrutinies
4 relate to our consideration for deferring donors who
5 have some geographic risk and our need to potentially
6 exclude them from the donor base? Let's show in the
7 next illustration. The number of donors that we have
8 deferred since the year 2000 now that we have
9 introduced additional scrutiny with regard to deferral
10 for attempts to decrease the likelihood of transfusion
11 transmitted CJD.
12 You can see that at our blood program in
13 the Dallas, Fort Worth area, we have now deferred
14 something like 3,500 donors, and this sad tally is a
15 significant underestimate of the actual number of
16 donors that have been deferred, and it is an
17 underestimate, because many of these donors are
18 individuals who have paid attention, taken heed of our
19 broadcasts, our announcements, our publications urging
20 them about the new restrictions. We have no idea of
21 what that number is. This number reflects only those
22 individuals who fail to appreciate the new
23 restrictions that we are publishing and who came to
24 donate anyway.
25 So what sort of contributions might these

1 individuals have made? Let's have the next
2 illustration. The next illustration. Thanks. How
3 many donations have these 3,500 individuals made?
4 Well, they have made something like 13,000 previous
5 donations, and these are individuals. These citizens
6 are now people who are indefinitely deferred. They
7 have obviously made important contributions to the
8 community blood program, and it is interesting that in
9 that conflict of interest questionnaire that was
10 handed out this morning, you were asked if you
11 regarded it as important that citizens affected by
12 decisions are directly involved in the Advisory
13 Committee process. And certainly, I believe that
14 citizens, in this case donors, are important and
15 should be involved, but they frequently do not get
16 that opportunity.
17 If you were to ask them how they respond
18 to their temporary or permanent deferral, let me show
19 you some of the questions that have been posed to us
20 during counseling sessions when we have spoken to
21 individuals deferred as a result of some geographic
22 exclusion.
23 Let's have the next illustration. This is
24 what we get posed. What should I tell my wife, my
25 husband, children, my dentist? What should I tell my

1 family practitioner? Where can I get tested? Where
2 can I get treated? Will this affect my medical
3 insurance, my disability insurance, my life insurance?
4 Will this count as a preexisting condition? Should I
5 reconsider having a family?
6 Let's have the next illustration. Why do
7 the criteria change? Other donors have asked
8 questions along these lines. So if I had been in the
9 UK for one day short of three months, I would be safe?
10 If you're telling me that I can't donate anymore, what
11 are you telling patients who got my blood? Why didn't
12 I hear about this from the military? How many
13 patients have got this disease from my blood? How
14 many patients have got this disease from a blood
15 transfusion anywhere?
16 Now, these are tough questions and
17 deferral criteria can be debated in the relatively
18 academic climate of these meetings, but justifications
19 for deferral that are acceptable here do not sit well
20 when they are explained to the donor community at a
21 lay level. The donor deferral process is essentially
22 a contributor and an important contributor to all
23 those layers of transfusion safety that we recognize
24 as being valuable, but the process is also responsible
25 for increasing numbers of former numbers whose

1 experience is marked by a sense of frustration and
2 alienation.
3 And this next illustration shows what has
4 happened to the rate of permanent deferrals amongst
5 blood donors in our community. You can see that
6 between 1999 and 2003, there has been a threefold
7 increase in the risk of permanent deferral of
8 individuals in the community. So just as we are
9 concerned about individuals who are temporarily lost
10 and our difficulty with getting them back, we are
11 concerned, too, about the fact that the rate of
12 permanent deferrals significantly contributed to
13 geographic exclusion is increasing so dramatically.
14 So in closing then, a few comments. For
15 many deferred donors, there is a credibility gap that
16 our explanations just do not bridge. And to avoid the
17 risk of transfusion safety being achieved at the
18 expense of availability of blood for transfusion,
19 CBER's Blood Action Plan that was promulgated in '97,
20 which addresses increasing the blood supply and
21 removing restrictions to safe donation really needs
22 our enthusiastic support and endorsement.
23 And then lastly, and this sincerely is not
24 meant as a plea for less safety or a plea for less
25 regulation, let me just say that it is easy to add

1 eligibility restrictions, and there are many recent
2 examples, smallpox, SARS, West Nile Virus, but the
3 more difficult task of lifting restrictions that no
4 longer serve a purpose is a task that also needs to be
5 addressed. Thanks.
6 SECRETARY FREAS: Thank you, Dr. Sayers.
7 Is there anyone else in the audience, at this time,
8 who would like to address the Committee on this topic
9 before the Committee?
10 MR. FILLBURN: Charles Fillburn, Nutramax
11 Laboratories. I would like to ask Dr. Hills, does he
12 exclude the possibility that the lone BSE animal that
13 was observed is not due to a mutation? Have you
14 sequenced the gene?
15 SECRETARY FREAS: Could you come to a
16 microphone, so our transcriber can record the
17 comments, please?
18 DR. HILLS: Bob Hills. Yes, we did look
19 at the spontaneous possibility, in other words the
20 mutation of PrP gene. What I can say is that we did
21 look at it. We have excluded it right now and for
22 other reasons, I really can't comment. There are some
23 publications coming out shortly with respect to that.
24 MR. FILLBURN: Do you think it's possible
25 that it could arise again either here or in the United

1 States simply as a consequence of mutation?
2 DR. HILLS: I --
3 MR. FILLBURN: The reason I ask is we seem
4 to assume that the only way this can occur is through
5 feed. If that's not the case, then we need to be more
6 aware that some of these restrictions that we're
7 putting on may be overkill.
8 DR. HILLS: Well, I think there are ways
9 that we can look at the PrP gene to determine whether
10 or not it is spontaneous mutation based on that. Now,
11 whether or not you can determine whether or not you
12 have sufficient testing power to ensure that that one
13 case you found is spontaneous or not, I don't know.
14 MR. FILLBURN: Okay. I would just like to
15 echo the comments of Mr. Vaz that in how we react to
16 the situation in Canada and our importation of any
17 products really has a dramatic -- can have a dramatic
18 effect on health care in the United States and it may
19 be an extreme overkill. I would like to see the USDA
20 and the FDA be on the same page in how they try to
21 treat this, that they be more realistic about it, and
22 demand more clearance work by processors who may be
23 dealing with these types of products.
24 SECRETARY FREAS: Thank you for your
25 comments. Do you have a quick comment?

1 MR. HAFFENDEN: I'll try to keep it really
2 quick. I would like to echo the same comments, the
3 same that was expressed by Mr. Vaz. We do collect,
4 have up until May 24th collected Canadian origin
5 animal-derived blood products that are sold into the
6 veterinary and pharmaceutical industry. We have
7 collections in Australia and in the United States.
8 These are critical supply raw materials,
9 and I believe that we do need harmony between USDA and
10 FDA on guidance. We also do have an isolated herd,
11 isolated BSE-free herd in Canada and would like to
12 volunteer to participate in a committee than can help
13 to set those guidelines and give some examples of what
14 is really there.
15 I understand why the USDA in particular
16 and the FDA have to react quickly and close doors, but
17 I believe we need to put the resources shortly to
18 analyzing products on a product by product basis, not
19 a global product entity, and reopen those doors for
20 products that are needed and critical.
21 SECRETARY FREAS: Thank you for your
22 comments. There will be two more open public hearings
23 tomorrow, and at that time, we will be more than glad
24 to welcome your comments.
25 CHAIR PRIOLA: This topic is open for

1 discussion by the Committee if anyone would like to
2 make a comment or have any additional questions. I
3 know I have one question that I actually forgot to ask
4 Dr. Hills. You said you ruled out the possibility of
5 this case having originating in Saskatchewan or no,
6 sorry, excuse me.
7 As a consequence of exposure to CWD or
8 scrapie, as well as as a consequence of a spontaneous
9 event, did you do that based on purely pathological
10 assessment or how did you come to the conclusion that
11 this was not a case of a cow coming into contact with
12 a CWD infected deer or elk, a scrapie infected sheep,
13 especially since Saskatchewan is where the CWD is,
14 right?
15 DR. HILLS: Yes. That actually was a
16 concern, which is why what we did when we sent the
17 sample over to Weybridge, we actually were asking them
18 to look specifically at the strain that they had in
19 hand and to compare that with the strains that they
20 had and they saw no differences.
21 DR. ROGERS: Ron Rogers, a little bit
22 more.
23 CHAIR PRIOLA: Okay.
24 DR. ROGERS: I just wanted to say that
25 some samples have been sent over to a stacks group in

1 the UK, and like they are doing a differentiation on
2 the glyco-civilization patterns, and so the CWD -- we
3 had already previously been involved with them in some
4 research activities to look at CWD profiling, I guess
5 you have to say at this stage. So this did have some
6 positive material over there already, and so this
7 material also was brought over to sort of see if, in
8 fact, we can get those kinds of patterns.
9 CHAIR PRIOLA: Okay.
10 DR. ROGERS: So it's purely at the
11 research level that this was ruled out.
12 CHAIR PRIOLA: So basically, right now,
13 pathological assessment, and you're doing the
14 molecular assessment of the PrP. Okay. Any other
15 questions or comments? Yes, Shirley?
16 MS. WALKER: I find that it is interesting
17 that Canada is now moving to provide the restriction
18 to add SRMs after reviewing their new case, and we
19 have just been asked to look at that language in our
20 present policy, so we might be cognitive of looking at
21 and changing our policy too quickly.
22 CHAIR PRIOLA: Okay. If there are no
23 other questions or comments from the Committee, then
24 I think we can move on to Topics 3 and 4, so the
25 remainder of the afternoon is going to be a general

1 introduction to TSEs and decontamination of medical
2 equipment and facilities. The first speaker will be
3 Dr. David Asher from the FDA.
4 DR. ASHER: Thank you. Well, it's a great
5 pleasure to open this session on decontamination of
6 TSE agents, which has been developed jointly by the
7 FDA Centers for Biologics and Devices. This topic is
8 presented, next slide, please, in response to a
9 request from this Committee last year for more
10 specific information before members felt comfortable
11 advising the Agency concerning appropriate
12 decontamination of tissue establishments where the TSE
13 agents might be encountered.
14 Next slide, please. FDA, of course, as
15 part of its mission, is responsible for helping
16 industry to keep regulated products safe and that
17 includes keeping products free of pathogens, today's
18 pathogen of interest, of course, the TSE agent.
19 Properties of the TSE agents complicate those efforts.
20 Thank you. You have already heard some discussion
21 about the context-dependency of inactivation of TSE
22 agents. I expect you will hear more.
23 Scrapie, of course, scrapie agent has not
24 been completely inactivated after exposure or after
25 drying and then exposure to steam heat. Fortunately,

1 TSE agents are substantially inactivated in solutions
2 of sodium hydroxide, sodium hypochlorite and probably
3 other chemicals. Hence, the World Health Organization
4 consultants have recommended decontamination in health
5 care environments using combined sodium hydroxide or
6 sodium hypochlorite and moist heat. Some other
7 authorities have doubted the need for such harsh
8 chemical treatments, and we would like the Committee
9 today to consider these different points of view.
10 The situations for which we are soliciting
11 advice today are for products regulated by the Center
12 for Devices, that is instruments and by the Center for
13 Biologics Instruments and Surfaces used in the
14 production of tissue products and plasma derivatives.
15 There are, of course, somewhat similar
16 though not identical situations that would involve
17 other centers, our Center for Drugs is particularly
18 interested in today's discussion, because, of course,
19 some drugs have components of human or animal origin.
20 We are aware that some of the problems involved in the
21 production of food or feeds are similar, but the
22 contexts are really quite different, for example, of
23 course, sodium hydroxide poses certain problems in
24 proximity to food products.
25 We would certainly logically expect that

1 some issues of the U.S. Department of Agriculture,
2 which regulates animal slaughter and meat production
3 in interstate commerce and the Environmental
4 Protection Agency, which regulates water affluence,
5 including affluence from autopsy rooms, that they
6 would have relative issues, but this Committee is not
7 advisory to those agencies, and we do not solicit
8 advice for those problems.
9 Next slide, please. There is no question
10 that contamination of classes of products regulated by
11 the Food and Drug Administration have transmitted
12 Creutzfeldt-Jakob Disease to human beings, fortunately
13 few, relatively few such cases have been recognized in
14 the United States.
15 Next. One such class of contaminated
16 products is reusable surgical instruments of which a
17 contaminated cortical electrode shown here in pieces
18 is the best known example.
19 Next slide, please. I am aware of only
20 six cases summarized here in which transmission of CJD
21 has been plausibly attributable to contaminated
22 surgical instruments, and I would note that in none of
23 those was modern cleaning or steam water used to
24 decontaminate the instruments involved.
25 In addition, at least two epidemiological

1 studies of which I am aware have claimed to
2 demonstrate some association with previous surgery,
3 though most studies have not found that and the
4 association is not particularly impressive.
5 Next slide, please. You have heard that
6 inactivation by heating of scrapie agent is very much
7 context-dependent. This is a slide of data from Bob
8 Rohwer some 20 years ago demonstrating that scrapie
9 infectivity in aqueous suspension was reduced to the
10 level of detection in less than five minutes at 121
11 celsius. That was carefully suspended in aqueous
12 solution. Although, at boiling temperatures,
13 although, there was also prompt reduction in
14 infectivity, a reduction, a resistant fraction, that's
15 the term of art for Dr. Johnson, a resistant fraction
16 remained.
17 Next slide, please. But when dried onto
18 surfaces, infectivity was readily detected even after
19 autoclaving for an hour at 134 degrees celsius.
20 Next slide, please. Dr. Rohwer, who will
21 be our second speaker in this session, has confirmed
22 that apparent-- or rather, Dr. Taylor who will follow
23 Dr. Rohwer has confirmed that apparent paradox, and
24 found that different strains of TSE agent in similar
25 preparations, at least, appeared to have differences

1 in thermal stability. The conclusion of those studies
2 were that in worst case scenarios, autoclaving has not
3 been validated to decontaminate all TSE agents
4 completely.
5 Next slide. A number of factors listed
6 here must be considered in deciding whether there is
7 a significant risk that a contaminated instrument
8 might transmit Creutzfeldt-Jakob Disease, including
9 infectivity of the contaminating material, the
10 reduction in activity achieved by cleaning and
11 decontamination, and the root by which a susceptible
12 individual is exposed and Martha O'Lone will talk more
13 about those things tomorrow. Our speakers later this
14 afternoon and tomorrow will address those and other
15 issues.
16 Next slide, please. Central nervous
17 system tissues for humans as for animals have been
18 consistently demonstrated to be infectious when
19 assayed in susceptible animals.
20 Next slide. But there is also -- next
21 slide, please. There is also a significant though
22 smaller likelihood that tissues of patients with
23 Creutzfeldt-Jakob Disease outside the central nervous
24 system, and that's not just Variant Creutzfeldt-Jakob
25 Disease, that is typical sporadic Creutzfeldt-Jakob

1 Disease, will have some infectivity found and here are
2 positive tissues listed.
3 Next slide, please. Of course,
4 fortunately, most human tissues, fluids, excreta have
5 never been found to be infectious.
6 Next slide. Although, confidence in the
7 negative results is somewhat tempered because of the
8 very small number of samples studied, and the fact
9 that the assays used were animal transmissions, and
10 there does appear to be some species barrier even
11 between human beings and primates, which might raise
12 the level of the limit of detection.
13 Next slide. Just a couple of examples of
14 really how small the number of tissues successfully
15 studied has been.
16 Next slide, and the next slide. In human
17 CNS tissues, the mean content of infectivity measured
18 in the NIH series was estimated to be about 105
19 primate intracerebral lethal doses per gram, but note
20 that one brain was found to be infectious at a
21 dilution of 10-8, and considering both that and the
22 species barrier, it might be prudent to assume such
23 high levels of infectivity for high-risk human
24 tissues, at least in an occasional patient.
25 Next slide. Because of the substantial

1 uncertainties attendant to the biology of the TSEs and
2 the properties of the agent effects of cleaning and
3 decontamination, advice offered to public health
4 authorities in the United Kingdom and the USA
5 concerning surgical instruments has not been
6 consistent, and I won't read these. But the UK CJD
7 Incidence Panel has advised incinerating instruments
8 exposed to brains of patients with known CJD where our
9 respected authority, Bill Rutala, whose is going to
10 speak later, has felt that cleanable critical or even
11 semi critical devices in contact with high-risk
12 tissues of CJD patients can be cleaned and sterilized
13 by autoclaving either at 134 celsius or 121 celsius,
14 etcetera. Our proponents of both points of view are
15 present here today, and we really would encourage a
16 discussion of these conflicting points or, at least,
17 apparently conflicting points of view.
18 Next slide, please. The two FDA centers
19 who developed today's program have generally relied on
20 advice concerning decontamination that came from a
21 consultation convened at the World Health Organization
22 in 1999 published the following year. That
23 consultation was chaired by Paul Brown, who was then
24 the chair of this Committee, and our next two
25 speakers, who are among the most influential of the

1 participants, are two of this Committee's former CDC
2 members, both of whom are in attendance today, were
3 also in attendance at that meeting. The consultation
4 identified recipients of potentially contaminated
5 products as being the group of persons at the greatest
6 risk of iatrogenic CJD.
7 Next slide, please. And they offered the
8 following general advice. They acknowledged that
9 decontamination is context-dependent and that one
10 method may not be completely effective in all
11 circumstances. Cleaning facilitates decontamination
12 using the best validated methods available,
13 essentially meaning based on actual pilot studies.
14 And then they advised using what we call an orthogonal
15 strategy, that is using two different methods, methods
16 based on different physical chemical principles
17 whenever that is possible.
18 FDA staff might add that in choosing those
19 orthogonal methods, that a method that inactivates the
20 agent is generally considered more reliable than one
21 that simply removes it, because when an agent is
22 removed, there is always the danger that it can be
23 reintroduced back into the product of interest.
24 Next slide, please. They recommended
25 single-use to instruments, destroying reusable

1 instruments wherever possible, but they acknowledged
2 that there are obvious situations in which instruments
3 simply cannot be discarded, and that less effective
4 methods than destruction may have to be used.
5 Next slide, please. The consultation
6 recommended a series of decontamination methods in
7 order of decreasing probable effectiveness.
8 Next slide. I expect that they
9 recommended six such methods. I won't go through them
10 all here. I expect that they will be discussed by
11 several of the speakers later today and tomorrow, but
12 note that the first four all include the use of either
13 sodium hydroxide or sodium hypochlorite either with or
14 followed by steam autoclaving.
15 Next slide. The last of the six was to
16 autoclave 134 celsius 18 minutes with the caveat that
17 in worst case scenarios, that is where brain tissue
18 has been baked, dried under surfaces, the infectivity
19 will be largely, but not completely removed.
20 Next slide, please. And for surfaces or
21 heat sensitive instruments, they recommended sodium
22 hydroxide or sodium hypochlorite at room temperature.
23 Next slide. A number of other treatments
24 listed here were dismissed as being inadequate.
25 Next slide. We tend to think of the

1 decisions regarding effective decontamination in these
2 four general categories, and I suggest that it might
3 be useful if the Committee addressed them in this way,
4 as well. The surface of these situations are surfaces
5 or instruments potentially contaminated with either
6 high-risk tissue or lower-risk tissue from a subject
7 with definite or probable TSE, and then the same
8 categories for someone where TSE is not suspected.
9 Next slide. We're fortunate to have with
10 us today Bob Rohwer, who has already spoken, David
11 Taylor to review the general principles of TSE
12 decontamination and the basis for the WHO
13 recommendations. Unfortunately, Dr. Philippa Edwards
14 of the UK, CJD Incidence Panel, is ill, but she kindly
15 emailed a talk for us, and that will be delivered by
16 Pedro Piccardo, who is an alumnus of this Committee
17 and a most welcome recent addition to our CBER staff,
18 dealing with TSE issues.
19 Bill Rutala, who is consultant to the CDC
20 on hospital infection control, will share his
21 extensive experience here in the USA. Ed Rau will
22 then report on interesting studies of incineration
23 that he and Paul Brown have been conducting. And
24 finally, today we'll end with Stan Brown of our Center
25 for Devices, and I, who will report some early results

1 of models that we have been studying based in part on
2 the work of Charles Weissmann, who will speak to us
3 tomorrow.
4 Next slide. Then tomorrow the issue for
5 discussion will be presented for CDRH by Lillian Gill,
6 Martha O'Lone and Charles Durfor, and for CBER by Ruth
7 Solomon and Dorothy Scott. Ellen Heck will review the
8 needs of Eye Bank. Christoph Kempf and Andrew Bailey
9 will represent the Plasma Proteins Therapeutics
10 Association in discussing the needs of plasma
11 processes, including a study that they will propose.
12 Please, note that, again, although the
13 discussions will doubtlessly be of great interest to
14 other agencies of the U.S. Government, and especially
15 to our Center for Drugs, we do not solicit advice for
16 these other agencies, only for FDA-regulated devices,
17 tissue products and blood products.
18 Last slide, please. With that, I hope
19 that you find the program that we have assembled
20 informative, and we anticipate having useful comments
21 during our open public hearing, and discussions and
22 votes by the Committee. Thank you very much.
23 CHAIR PRIOLA: Okay. Thank you, Dr.
24 Asher. Our next speaker will be Dr. Bob Rohwer.
25 DR. ROHWER: Thank you, and let me begin

1 with an apology to those people who have heard this
2 talk before. It is one that I have given to this
3 Committee actually in an earlier form of it in the
4 past, and have given it fairly frequently over the
5 last few years, but I was asked to do it again just
6 because David felt that the place needed revisiting.
7 And so we'll begin with the first slide.
8 The main points I'm going to make in this talk are
9 that the susceptibility to inactivation of TSEs
10 infectivity is within the normal range for viruses and
11 spores, but that the TSE infectivity is resistant to
12 disinfection or sterilization. That may seem like
13 incompatible statements, but I will try to show you
14 what I mean in just a minute.
15 The susceptibility to inactivation is an
16 intrinsic property of the agent, and this
17 susceptibility is normal. That's what I'm saying, but
18 the resistance is context-dependent and a property of
19 the environment of the infectivity.
20 Next slide. The best sources for this at
21 the current time are these old papers of mine in
22 Science and Nature, which have the complete
23 experiments behind the kinetics that I'm going to show
24 you here and this review, which puts it into a larger
25 context.

1 Next. And then the WHO report, which Dr.
2 Asher just reviewed is also a very excellent source.
3 Next. I am going to begin by just talking
4 about the inactivation process itself. And this is
5 actual data taken from an activation process with the
6 scrapie agent. This is was a hypochlorite experiment,
7 I believe. I have forgotten now. I put this together
8 so long ago, but the main points are the following.
9 If I can have the next. We're going to
10 build this slide as we go through it. The
11 inactivation process, one way to think about this is
12 if we think of this is surviving fraction on this axis
13 over here where we start with 100 percent survival, no
14 killing. At 10-1 survival, we have destroyed 90
15 percent of the population.
16 Next slide. So for example here, I mean,
17 here we're starting. If we convert this to a 100
18 individuals, what we have got by the time we're here
19 on this inactivation curve is only 10 percent of the
20 population left. We have killed 90 percent of the
21 population in these very first moments of exposure,
22 and by the time we get to the second log of
23 inactivation, we're down to one out of 100 survivors.
24 This is just by way of review of things that you
25 probably had in your elementary chemistry class, but

1 we sometimes forget this with time.
2 Next. And then if we look down here, we
3 notice that 90 percent of the kill occurs during this
4 first tiny interval. Only 10 percent of the kill
5 occurs during this next interval. Only 1 percent
6 during this, a 10th of a percent, a 100th of a percent
7 during this interval right here. We're getting less
8 and less effect as we go along. The vast majority of
9 what is happening to this population is occurring
10 right here in the very first moments of exposure.
11 Next. And this is reflected by this
12 component of the inactivation, which is reflected by
13 this line right here, and the inactivation rate
14 constant for this line is the inactivation rate
15 constant, which is defining the behavior of the vast
16 majority of the individuals in this population.
17 Next. Next. This line describes a second
18 component, and it is describing, next, a much smaller
19 proportion of the population. About one in 10,000 of
20 the individuals behaves like this.
21 Next. So what is going on here? We have
22 susceptibility to inactivation as defined by this
23 initial rate of inactivation, is intrinsic to the
24 agent. It is actually less complex and there are
25 fewer controlling parameters. Whereas, over here,

1 this population that is being inactivated at a
2 different rate could be gaining those properties in a
3 number of context-dependent ways, and these are
4 different for each environment and they are much more
5 complex.
6 It could be due to the container. It
7 could be a factor. I mean, it could be any
8 combination of these factors, as well, but among the
9 things that we have to consider are the container,
10 rough or smooth surfaces, reactive surfaces, porous
11 surfaces, cofactors like fats, proteins, oxidants,
12 reductants, water, air, in the case of autoclaving,
13 buffers, pH, temperature can all affect the
14 inactivation suspension, whether what the source of
15 the tissue is and its composition, the procedure for
16 making it, how it was homogenized, the dose rate,
17 various transfers.
18 And then we have these kind of procedural
19 problems with making these measurements themselves,
20 which are the accuracy limitations of the assay and
21 its reproduce-ability. This is a real issue in the
22 case of end point dilution titration of TSE
23 infectivity, which is only good to about .3 logs. And
24 cross-contamination is an issue, and it becomes an
25 especially important issue when we're talking about

1 very low levels of survival at the very end of these
2 inactivation curves.
3 How do we know that this survival isn't
4 due to something that got transferred from here, which
5 has almost 100,000 times more infectivity in it? The
6 way we know is we're very careful when we do these
7 experiments, but it's something that you have to be
8 very careful about.
9 Next. Next, please, and next. Let's go
10 to the next slide. Click through to the next slide.
11 Thanks. In comparing agent properties, the properties
12 that are intrinsic to the agent are reflected in the
13 initial rate of inactivation. That is when the vast
14 majority is being inactivated, and the interpretation
15 is less complex. The size of the residual fraction is
16 a complex function of environmental parameters, and
17 cannot be used to compare the intrinsic sensitivities
18 of agent strains.
19 This is where I differ with Robert's
20 perspective that he gave this morning. In other
21 words, I consider these plateaus to be a very
22 important public health and agricultural problem in
23 terms of infection control, but they are not telling
24 us that much about the intrinsic properties of the
25 agent. They are telling us about the context of the

1 agent. They are telling us something about the
2 context of the agent, and it has been very difficult
3 for us to figure out what that is.
4 Next. So let's consider an example from
5 chemical inactivation.
6 Next. This is a hypochlorite inactivation
7 in which we can see that. In the scrapie curve right
8 here, we have -- this is surviving fraction, the same
9 kind of curve I just showed you minutes ago down here,
10 that on contact with hypochlorite, .5 percent, this is
11 a normal concentration, which bleaches use, and we get
12 an initial very rapid killing down to about 3 logs,
13 but then we hit a plateau and there is at the level of
14 1 part per 1,000 or a 10th of a percent, we have got
15 something in this population that is protected from
16 hypochlorite. It's not seeing it.
17 By the way, we checked. The available
18 chlorine did not change significantly over the course
19 of this infection. We did this same experiment with
20 some controlled viruses. These are bacteria phages.
21 They are non-involute viruses. They are very easy to
22 assay and they are reasonably robust in some ways and
23 not others. But here is PhiX 174 showing the exact
24 same phenomenon. It plateaus at a lower level. FD
25 and M13 like phages doing the same thing over here.

1 Here are these two. These two viruses
2 were spiked into the same kind of normal brain
3 homogenate that the scrapie brain was in, and they
4 exhibited this behavior in a purified form in PDS.
5 They were inactivated to the limit of detection almost
6 instantly on contact with bleach. Another example of
7 context.
8 Next. Next, please. Well, two of the
9 things that we are going to discuss here are the
10 things that work best for TSE agents, and bleach is
11 one of them, and I hope that David will be sharing.
12 He has a lot more data on bleach than I do, and I hope
13 he will be sharing that with us. But sodium hydroxide
14 is something that I have been pursuing for a long
15 time, and this was an experiment a long time ago with
16 Paul Brown, one of our initial experiments, comparing
17 CJD and 263 scrapie.
18 Again, in a very highly dispersed 10
19 percent brain homogenate of these two infectious
20 agents, and adding sodium hydroxide at these
21 concentrations, and I would just ask you to
22 concentrate on these first three lines here. At 60
23 minutes with one normal, we had limited detection
24 killing here and here for both CJD and scrapie. By 15
25 minutes, we had almost as much inactivation. A 10th

1 normal did almost as well as one normal. It's a very
2 effective method.
3 On the other hand, next slide, please,
4 this is a table of -- it's now out of date. There are
5 more experiments would could be put on here, but at
6 the time I made this, these were all the sodium
7 hydroxide experiments that were in the literature, and
8 we got very, very good inactivation by sodium
9 hydroxide, but there are examples here. These are the
10 experiments that we had done, at that time, but there
11 are examples here where there is some activity left
12 after considerable amount of exposure, and that always
13 was very puzzling to me, but my guess is that it has
14 to do with how the stuff is presented and homogenized.
15 Next. I went back and revisited. We have
16 revisited this subject with a kinetic experiment on
17 sodium hydroxide, which is presented here. And in
18 this case, the black circles indicate infectivity, and
19 this is time of exposure, and we're seeing something
20 that is very similar to the sodium hypochlorite
21 effect, except much more dramatic even. We're getting
22 a huge reduction on contact, essentially, with sodium
23 hydroxide. This is the point that was taken in the
24 shortest amount of time, interval, that we could
25 effect between adding the sodium hydroxide and then

1 adding the acid to neutralize it, and then taking the
2 points. So it's right around 30 seconds. This is two
3 minutes, etcetera.
4 But on this same curve, I have got two
5 other plots. One is a plot, which I am labeling
6 denaturation in one hydrolysis. And what do I mean by
7 that? Well, we went back later and used a Western
8 Blot on these samples to see whether we could recover
9 Western Blot signal or not from these various
10 fractions. And the Western Blot, especially at the
11 time that we did this, was not as sensitive as the
12 infectivity assay, so we couldn't detect it over as
13 long a range, but it was very clear that upon contact
14 with sodium hydroxide, we destroyed the pk resistance
15 of PrP. It was gone. It was showing the same
16 inactivation kinetics, essentially, as the
17 infectivity.
18 Whereas, if we didn't pk digest and we
19 just put the stuff on the gel to see whether there was
20 anything left, it also disappeared, and this is a
21 disappearance by hydrolysis. The protein is being
22 hydrolyzed. It no longer shows up on the gel, and it
23 is showing quite different kinetics. So one of the
24 points that we can take home from this is that to the
25 extent that infectivity and PrP are related and the

1 prion protein are related, and I am not entirely
2 convinced of that, but nevertheless, to the extent
3 that they are, it's denaturation that is the correlate
4 with inactivation of infectivity not hydrolysis. This
5 is basically good news, because it's much easier to
6 denature something than hydrolyze it.
7 Next. Heat inactivation will be the next
8 topic.
9 Next. This is a -- I have just taken the
10 121 degree autoclave experiment out of that family of
11 curves that Dave just showed you and that I showed you
12 earlier in the day, because it makes the points best
13 in my opinion. Here is a case where, at the time we
14 did this experiment, the story was that you couldn't
15 kill this stuff with autoclaving, you know, that 121
16 degrees was not sufficient to destroy the infectivity
17 from 263K hamster scrapie.
18 This is a kinetic experiment showing that,
19 and this was done not in an autoclave. It was done in
20 an oil bath. The samples were sealed in ampoules.
21 They were plunged into the oil bath, so that we could
22 control their -- and I was using thermistors, at that
23 time. The temperature was being recorded, so I knew
24 when they got to 121 degrees. I knew what the ramp
25 time was. I had that on my recorder, and we could

1 control the actual time of exposure within very narrow
2 limits.
3 So this first point on this curve was
4 taken after the 58 second ramp time to 121 degrees, so
5 it had just got there. By the time it got to 121
6 degrees, we had already destroyed 99.9999 percent of
7 the infectivity in that sample. On the other hand, it
8 took another 10 or 15 minutes to get to the limit of
9 detection of the infectivity. There was a residual
10 population that took longer.
11 And this is a concern, and this was a very
12 highly dispersed sample again of infectivity, and you
13 get quite a different story, next, please, if you do
14 this type of experiment. Now, I think David is going
15 to be showing a lot more of this in a few minutes, but
16 later on, David Taylor started doing these experiments
17 using brain macerates. Now, this is not a homogenate.
18 This is a mush of brain. It is not dispersed in
19 fluid. It's a paste, basically, and it is being
20 exposed at these various temperatures in the
21 autoclave, and this is the untreated sample, and these
22 samples are getting incomplete killing even after
23 these very extreme treatments. I mean, this is quite
24 extreme for steam inactivation.
25 Well, you definitely have to say that this

1 poses -- you wouldn't want this on your scissors when
2 they go back into the next patient, for example. This
3 is an extremely important public health result. On
4 the other hand, what does it tell us about the agent
5 in what we're dealing with? Well, you can get a titre
6 out of this, because you're at limiting dilution here,
7 and we can do something we call a parson, we get a
8 parson titre out of this type of sample. This is how
9 we make our measurements in low titre blood samples.
10 And I have done this on the next slide and
11 just put these figures on next. This is where these
12 samples would fall on this curve that I just showed
13 you. There has still been an extremely high level of
14 inactivation associated with these, but you have got
15 survival going all the way out to 134 degrees here, at
16 134 all the way out to 60 minutes for some of these
17 samples that were done in these macerates.
18 Personally, I think we're talking about
19 the same story here. It is just a matter of what
20 we're talking about, and the context has been ramped
21 up in the case of macerates versus homogenates, and
22 the survival lingers for longer periods of time.
23 Next. Next, please. So what are we
24 dealing with here? These could be intrinsic
25 differences, and that was a question that came earlier

1 in the day from Dr. Bailar and it's a legitimate one.
2 I think it needs more study. A lot of us have this on
3 our books. Robert said he has been planning to do
4 this. I have been doing it. I have got these samples
5 in the freezer. I just have not gone back and redone
6 this experiment, redone the kinetics on these, but it
7 is on the books. Someday, it will get done.
8 But when you talk about these heritable
9 differences, the point that I want to emphasize is
10 that I feel that they have to be discussed on the
11 basis of inactivation rate, not residual infectivity.
12 And my own prejudice is that the rates will be exactly
13 the same, because what we're dealing with here is
14 context, not intrinsic differences.
15 Aggregation is another issue. This is
16 something that I was very interested in early on in my
17 career, but I think we have this under control at the
18 moment with the way we are homogenizing and dispersing
19 things, and aggregation would give you a recognizable
20 difference in the inactivation kinetics. It would not
21 look like first order. It would be first order with
22 a delay. There would be a delay in something like
23 that contributing to that.
24 The most likely reason for this, in my
25 opinion, is compartmentalization. The inactivant is

1 not actually reaching the infectivity, and our
2 challenge before us is to find ways to open and
3 destroy this compartment to get at the infectivity.
4 Next. I just have a couple more here. So
5 if we compare these two moduses of investigation, what
6 we are using is 10 percent homogenate sonicated highly
7 dispersed versus whole brain macerate. This is sealed
8 in a serum bottle. I can't remember, David. Do I
9 have this wrong? I think David will correct me if I
10 have got this not exactly correct here on how he has
11 got these set up. We are using an oil bath versus an
12 autoclave. Our samples were being constantly stirred
13 while we were inactivating them versus static. And,
14 in fact, this is kind of an idealized type of
15 inactivation to get at the properties of the
16 phenomenon. Whereas, this is a worst case scenario,
17 which gets at the worst case problems that might be
18 confronted in the public health or agricultural
19 context.
20 Next. Okay. Now, we had some dry heat
21 data earlier in the day from Robert Somerville, so I'm
22 not going to go over this, except to say that if you
23 dry this material onto a surface, the inactivation
24 properties become completely different. It becomes
25 much, much more resistant to inactivation. However,

1 this isn't a completely unfamiliar phenomenon. It
2 happens with spores and it happens with other
3 microbes, as well.
4 Next. And so, in fact, my own
5 interpretation of this in a nutshell is that what is
6 happening in these experiments and where the source of
7 residual infectivity may be coming from in our ampoule
8 type of experiments is that as we stick our ampoule
9 into the oil bath, it boils and flashes off
10 immediately, and we throw things up on the walls and
11 they dry. We get little specks drying on the walls.
12 I was very religious about trying to recover
13 everything when I went back to reanalyze this
14 material, so I scraped the walls and got everything
15 back into the test tube.
16 And what if what is happening is we have
17 the infectivity in a form in which it is basically
18 anhydrous. We have little drips and drops here that
19 end up in little droplets of fat. Fat when it is
20 oxidized becomes a varnish, which is, essentially, a
21 plastic. And so, basically, what we're subjecting
22 this to is a dry heat sterilization at the rate of
23 parts per million in our case. It's not something
24 that's happening very often, but we create a dry heat
25 environment for a very small part of this infectivity,

1 and that is what is escaping. If the reagent can't
2 kill it, if you can't reach it, you can't kill it.
3 The other example I like to give is that
4 if you put brain homogenate in a Zip Lock bag and
5 throw it into one normal sodium hydroxide, nothing
6 will happen to that either. And so it has to be
7 available.
8 Next. Next, please. Next. Not that one.
9 That's not supposed to be there. So the point I want
10 to make here is that 132 degrees uses a significantly
11 higher temperature than 121 for steam sterilization
12 where the inactivation takes place in minutes or even
13 seconds, but 132 degrees is only incrementally more
14 effective than a 121 degree centigrade environment for
15 dry heat sterilization where the inactivation takes
16 hours to days at those temperatures depending on what
17 you're talking about.
18 So this does form, I think, a
19 rationalization for what we're seeing in this
20 situation, and it also tells us -- and this was the
21 rationalization for trying to remove all headspace
22 from those devices in which we did the gelatin
23 inactivations that I showed you this morning. We
24 didn't want any opportunity, any place for drying to
25 occur.

1 Next. I think there is just two more.
2 Steam sterilization, the agent is not intrinsically
3 resistant to steam sterilization. There are problems
4 with delivery.
5 Next. And for effective delivery, we
6 recommend surfactants, homogenization, high levels of
7 dispersion, eliminate sanctuaries, agitation is
8 helpful. My guess is that a refinant will also reduce
9 the potential for protective associations and will
10 improve the ability to inactivate.
11 Next. Prevent drying, immerse in water
12 prior to enduring steam sterilization and combine two
13 or more methods. And the processing details can be
14 critical. Adhere closely to validated approaches, and
15 this is referring to this stainless steel result we'll
16 hear more about tomorrow.
17 And where we should go with this. We need
18 to know more about the underlying principles of
19 resistance, and we definitely need more robust methods
20 for sterilization, which will actually get at these
21 last little bits of infectivity.
22 Why don't you end right there, and let me
23 just end by saying that the way we inactivate in the
24 laboratory, our own instruments, is for stainless
25 steel and things that can take it and things that are

1 recycled and go back into animals, immediately after
2 use they go into one normal sodium hydroxide. They
3 are immersed in one normal sodium hydroxide for at
4 least an hour, and then if they can take it, they are
5 put through the autoclave under one normal sodium
6 hydroxide. They are cleaned after decontamination
7 under those conditions, and then they are reprocessed
8 in sterile packs back into the facility for further
9 use.
10 CHAIR PRIOLA: Okay. Thank you very much,
11 Dr. Rohwer. Are there any questions before we move on
12 to Dr. Taylor? Okay. If there are none, we'll go on.
13 Oh, I'm sorry. David, go ahead.
14 DR. ASHER: Can you comment on aluminum
15 vessels, please?
16 DR. ROHWER: I didn't hear that.
17 DR. ASHER: Aluminum vessels.
18 DR. ROHWER: I still didn't hear it.
19 DR. ASHER: Can you comment on the use of
20 aluminum vessels?
21 DR. ROHWER: Oh, yes, right. We use a lot
22 of sodium hydroxide in our environment, and we learned
23 early on that you don't mix sodium hydroxide with
24 aluminum. And, in fact, aluminum and sodium hydroxide
25 in an autoclave can explode and can be quite

1 dangerous, so you have to be very careful about that.
2 So we, essentially, have no aluminum in our BL3.
3 CHAIR PRIOLA: I think I'll check our BL3.
4 I'm not sure if we have aluminum. Dr. Taylor, if you
5 would? Our next speaker is Dr. Taylor, and he is
6 going to talk about decontamination of TSE agents and
7 the WHO recommendations.
8 DR. TAYLOR: Thank you very much. Well,
9 thank you for the invitation to speak this afternoon.
10 As you can see, coming from the UK, I'm using thumb
11 roll technologies, slides and overheads. I was warned
12 there could be problems with the electronic system, so
13 I didn't bother with the front-line. I just brought
14 the backup.
15 As has already been discussed and as this
16 group will appreciate, there has been accumulating
17 evidence over decades that TSE type agents are
18 remarkably resistant to a wide variety of
19 decontamination methods, which are quite effective
20 with conventional microorganisms. This does not mean
21 to say that these methods have no effect, but rather
22 that they are impractical for usage in medical
23 settings, etcetera. These include things like strong
24 oxidizing agents, phenolic disinfectants and even
25 ionizing radiation.

1 Because of this general resistance, there
2 have been some known examples of iatrogenic
3 transmission where instruments or devices that were in
4 contact with the brains of CJD infected individuals
5 went on to cause accidental transmission in subsequent
6 patients despite having been processed in some fashion
7 or another.
8 Now, I use the phrase in some fashion or
9 another advisably, because the methods that were used
10 would not, in fact, be used nowadays, but David Asher
11 showed you the x-ray of implantation electrodes, which
12 would be put into a marmoset to look for infectivity
13 after this was suspected of causing this disease in
14 humans through accidental transmission. In this case,
15 the electrodes were washed in benzine and in a well
16 meaning exercise to try and sterilize them, they were
17 then exposed to alcohol and formaldehyde, which we now
18 know is not terribly good as far as TSE agents are
19 concerned.
20 The second example, which David Asher also
21 listed, was instruments used on a suspect case of CJD,
22 neurosurgical instruments, I should say, were exposed
23 to hot air, 180 degrees centigrade, for two hours
24 before reuse, and there was transmission from patient
25 to patient.

1 Now, as I said, and as David Asher
2 referred to, there is actually no convincing evidence
3 that we have seen accidental transmissions through
4 neurosurgical instruments, but some data suggests
5 epidemiologically that there is perhaps some evidence
6 of this, but there is no hard and fast evidence.
7 Nevertheless, with such dreadful diseases
8 that are incurable, untreatable, there has been a
9 constant nagging doubt about transmission of CJD. To
10 some extent, this was aggravated when Bob Will
11 reported in the UK the emergence of Variant CJD. As
12 you know, the number of cases has risen into the
13 hundreds now and is still mainly confined to the UK.
14 The worrying aspect of that, of course, was that the
15 work of Moira Bruce clearly demonstrated that the
16 agent causing Variant CJD was identical to the BSE
17 agent in cattle and quite dissimilar to any other TSE
18 agent that had ever been discovered.
19 Concerns regarding accidental transmission
20 of Variant CJD between patients was elevated by the
21 finding that New Variant CJD lymphoreticular system
22 tissues in the patient examined, infectivity or at
23 least positive PrP was detected with 100 percent of
24 these samples compared with nil percent of the
25 iatrogenic sporadic cases that were examined or in

1 other controls. That was a study here.
2 We also know that in a limited number of
3 studies, if you have archival tissue from patients who
4 end up with Variant CJD, in this case, appendix. You
5 can find PrP in the appendix at the time when the
6 patient had no clinical signs of disease. So the
7 potential for accidental transmission through surgery
8 is, at least, in theory enhanced by the fact that
9 surgeons compared with neurosurgical would much more
10 commonly be invading lymphoreticular tissues either
11 deliberately or incidentally.
12 Now, I would like to just show a few
13 overheads if I may. Both David Asher and Bob Rohwer
14 referred to the WHO meeting in 1999, which resulted in
15 guidelines being issued. It was related to not only
16 clinical aspects of CJD-like diseases, but also to
17 concerns for the practical issues, such as protection
18 of laboratory staff, pathologists, surgeons, etcetera.
19 Now, within the guidelines, there is this
20 table here, which you may not all be able to see,
21 which is almost a short form of what I started with,
22 talking about ineffective methods. And the only thing
23 I would say here is that I will go in to talk a little
24 about this procedure here, which is regarded as
25 variably or partially effectively boiling in 3 percent

1 sodium dodecyl sulfate, SDS, because this has been
2 commonly banded around as a probably relative
3 effective procedure.
4 In terms of the actual processes
5 recommended, and David Asher did show you a summary of
6 this, incineration, I will say nothing about, because
7 there will be something said about that coming up
8 shortly. These procedures, they were based on what
9 was known from the literature on TSE inactivation at
10 the time of the meeting. To my knowledge, not much
11 has happened since then to alter the views and
12 recommendations in these guidelines, and they are
13 listed in their perceived order of effectiveness.
14 So we start with emersion in sodium
15 hydroxide and heating in an autoclave, as opposed to
16 going on here to immersing in hydroxide then
17 transferring into water and going on to autoclaving.
18 Also, here, the alternative is to immerse in sodium
19 hypochlorite, and then going on to autoclave.
20 Here, we have emersion in hydroxide or
21 hypochlorite, and then going into an open pan and then
22 autoclaving. This is because one of the options here
23 is the 134 degree centigrade porous load cycle in
24 which you cannot put fluids. So if you're putting
25 instruments through these after the fluid treatment,

1 you must remove them from the fluid.
2 We then go on to suggestions for boiling.
3 These are listed in order of decreasing perceived
4 effectiveness, bearing in mind that WHO
5 recommendations are, essentially, for the health
6 community worldwide, and that facilities and equipment
7 availability will vary tremendously, especially in
8 some more deprived areas of the world.
9 Finally, we go on to talk about
10 autoclaving at 134 for 18 minutes. And then when it
11 comes to things like surfaces, we revisit procedures
12 like sodium hydroxide and sodium hypochlorite. Then
13 you can just do thorough cleaning if you can't do
14 anything else. And then there are some questions
15 about dry goods and autoclaving.
16 So I have been asked to address or discuss
17 with you the data, in a sense, that we use to back up
18 these recommendations, which I will do and finish with
19 one or two bits of additional, perhaps anecdotal
20 information.
21 Will you go back to the slides now,
22 please? I did mention that I would talk briefly about
23 SDS, because simply boiling in sodium dodecyl sulfate
24 or concentrations as low as 3 percent has been widely,
25 well, fairly widely recommended as a very effective

1 procedure. However, in our own experiments where we
2 used 5 percent of this compound and even went on to
3 autoclave at 121 degrees centigrade, we certainly did
4 not completely inactivate.
5 Now, we did get down to almost a limiting
6 dilution. In other words, we have reduced infectivity
7 probably in the region of 10,000 fold or something
8 like that, but within a medical care context to have
9 surviving infectivity at this level would be a
10 concern. And so I present this simply to discuss an
11 idea that hot SDS is a universal panacea.
12 Now, Bob Rohwer discussed with you his
13 hydroxide data that he co-published with Paul Brown in
14 1986, I think, and he also showed a list of, if you
15 like, some contradictory data. These are
16 publications, which are all saying much of the same
17 thing, and that is that sodium hydroxide looks to be
18 pretty effective, but not completely so. A suggestion
19 is that you are knocking down infectivity, because
20 this is at room temperature, by the way.
21 And the one comment I would make to Bob
22 about certainly our experiments compared to his, I
23 can't talk for many of the others, but clearly, you
24 found complete inactivation, but we didn't know it.
25 It's acknowledged in your paper that the sensitivity

1 of your assays were slightly reduced because of the
2 toxicity of the hydroxide to the examples. In other
3 words, you diluted these to make them so that they
4 could be tolerated by the hamsters.
5 In our own experiments, what we found is
6 that if we fiddled around considerably, we could
7 actually neutralize, get the pH down to neutral in the
8 end products, and provided they were injected very
9 quickly into the brains of mice, we didn't need to
10 dilute. So there is a slight difference in
11 sensitivity between the tests. I'm not saying that is
12 necessarily the explanation, but it is possibly so,
13 because we do have a solid bank of data saying cooled
14 hydroxide is not completely effective.
15 Right. In our own studies, what we found
16 was that after exposure and, again, room temperature,
17 this is a hamster agent, one molar hydroxide, two
18 molars for two hours. We brought the infectivity
19 level something down, certainly, but we were left with
20 about 4 logs of infectivity.
21 Now, if we combine the hydroxide treatment
22 with heat as has been recommended, then, in fact, we
23 find complete inactivation either when you add
24 hydroxide to the samples and immediately autoclave or
25 when you hold in hydroxide for an hour and then go and

1 autoclave. And in other studies, such as those from
2 the Rocky Mountain Lab, they found that if you held in
3 hydroxide, then neutralized the pH and went on to
4 autoclave, you still got inactivation.
5 And these are the various publications,
6 which all come to the same viewpoint, somewhat unusual
7 in TSE studies to have so many publications saying the
8 same thing, that hot hydroxide is effective, whether
9 this is a sequential process or whether the hydroxide
10 treatment is at the same time as your autoclaving.
11 Now, in terms of sodium hypochlorite,
12 which is one of the recommended procedures, we did
13 some studies quite some time ago with two strains of
14 mouse agent exposed to sodium hypochlorite containing
15 various concentrations of available chlorine, and we
16 found that once you got up to about 8,250 parts per
17 million of available chlorine, you had a complete
18 effect.
19 Now, the data here, and these were studies
20 that were done on behalf of the Department of Health
21 in the UK some time ago, and being extremely
22 conservative, the Department of Health accepted the
23 data, but said well, to play it safe, we'll make the
24 recommendation that you should use sodium hypochlorite
25 containing 20,000 parts per million of available

1 chlorine, which considerably exceeds the lowest levels
2 of efficiency here, but that's where the
3 recommendation came from to use 20,000 parts per
4 million.
5 Somewhat later, using two sources of BSE
6 infected cow brain, we tested sodium hypochlorite once
7 again. Alongside it, we also tested sodium
8 dichloroisocyanurate, which is another chlorine
9 releasing compound, which is generally considered to
10 have a comparable efficiency compared with
11 hypochlorite when compared at the same levels of
12 available chlorine.
13 In these studies of these various
14 concentrations of available chlorine, there was no
15 infectivity detected in any of the BSE cow brain
16 samples treated with hypochlorite. But when you
17 looked at the samples treated with the
18 dichloroisocyanurate at comparable levels of available
19 chlorine, there were, in fact, a significant number of
20 positives.
21 This came as rather a surprise, but we
22 found then by doing assays on the chlorine content
23 left after the exposure periods, that the sodium
24 hypochlorite compared with the dichloroisocyanurate,
25 if you look at the starting and finishing

1 concentrations of chlorine, the hypochlorite much more
2 readily gave up its available chlorine during these
3 decontamination procedures compared with this
4 compound. It may be that longer exposures might be
5 effective, but we are already up to two hours, which
6 it's getting a bit impractical to extend things beyond
7 that.
8 Mention was made of boiling. Well, we
9 certainly do have data, which have only actually ever
10 appeared in an abstract sort of meeting. They have
11 never been formally published, but we did find with
12 301V, that if you boiled for one minute, that we have
13 no detectable infectivity left compared with material
14 exposed to hydroxide at room temperature or microwaved
15 for one minute.
16 Bob mentioned the data produced based on
17 134 to 138 degrees centigrade porous load autoclaving.
18 This was in either BSE infected cow brain, scrapie
19 infected sheep brain or scrapie infected hamster
20 brain, and we had survival rates as shown here, which,
21 as Bob suggested from this graph, fall pretty far down
22 on his survival curve. And, indeed, when we titrated,
23 the starting titre here again was 9 and a half logs.
24 It came down to about 2 logs or less. So substantial
25 inactivation, but, in fact, in terms of health care,

1 still a worrying amount of infectivity left.
2 In terms of more recent studies using
3 301V, we had really surprising data for this
4 experiment where we autoclaved either at 134 or 138
5 degrees centigrade for these periods of time with
6 these weights of tissue. Now, the norm is, of course,
7 as you increase autoclaving time and/or temperature,
8 you expect the efficiency of decontamination to
9 increase.
10 In these studies, the reverse was true.
11 In fact, we had more cases of TSE in the case injected
12 with the samples from the 138 compared with the 134
13 process, which was statistically significant. If done
14 on a one off basis, I would have had severe doubts
15 about the technical quality of our experiments here,
16 but, in fact, we had other experiments running at the
17 same time, which showed the same trends, perhaps not
18 so impressively as here, but definitely showed the
19 same trends.
20 Also, there were studies being carried out
21 on behalf of the Department of Health who insisted
22 quite correctly that all of the equipment and the
23 processes should be independently monitored. And so
24 we had a third party monitoring the progress of these
25 experiments, thermocoupling of blanks for every single

1 stage of the process. And there are some of you that
2 know there is still, I think, a T-chest full of trace-
3 outs for all these experiments. So I have no doubt
4 that we're seeing a genuine trend here.
5 I mentioned that we're using 301V and we
6 do know, as Robert Somerville mentioned this morning,
7 that 301V within the spectrum of the agents that we
8 have tested is certainly far more thermostable than
9 others. These strains here are all most precise
10 scrapie agents. 301V is our most precise BSE agent.
11 There is a survival after autoclaving and the blue
12 bars are the untreated samples. And you can compare
13 the titre losses with the different agents after the
14 autoclaving process.
15 My take on what was happening in these
16 experiments was that in the past where we found much
17 more efficient inactivation or in some cases, complete
18 inactivation, we often used intact pieces of brain
19 tissue. In the more recent experiments, as Bob Rohwer
20 said, we were using brain macerate. This is undiluted
21 brain, which is just mixed up, so it's a homogenous
22 sample to give you a blancmange like material for
23 autoclaving.
24 Now, in putting these samples into what
25 Ron described as long neck tubes, not terribly long

1 neck, but there is almost inevitably some smearing and
2 drying of the infectivity onto the tubes before you
3 get to the autoclaving stage.
4 My concept, my take of what is happening
5 and what explains the results is that during the
6 porous load autoclaving process, which I must tell
7 you, unlike the gravity displacement system where
8 there is usually a slow buildup of steam, the porous
9 load system involves a huge and rapid admission of
10 steam into the chambered autoclave, which, in my
11 simple hypothetical structure here, is able to fix any
12 proteinaceous material in these fringes, and that
13 paradoxically, if that protein is PrP protein, the
14 actual fixation process, which occurs early and
15 rapidly at the beginning of the steam process actually
16 protects that infectivity from the subsequent
17 sterilization of the steam effect.
18 If that was so, that would explain why the
19 138 degree samples were more positive than the 134
20 since you would expect the rapidity and efficiency of
21 that heat fixation to be greater at 138 compared to
22 134. I hope to show you in the next few slides that
23 this is not all quite cuckoo land.
24 We do know that if you fix infectivity or
25 fix infected tissues with formaldehyde, you make that

1 infectivity colossally more resistant to inactivation
2 by autoclaving. Here, we have 50 milligram fragments
3 or whole mouse brains that are infected with the
4 strain called 22A, fixes in formalin and then
5 autoclaved. And, in fact, 100 percent of the
6 recipient animals have gone down in disease. Whereas,
7 in these experiments, we were completely able to
8 inactivate infectivity in these samples if they were
9 simply emerged in saline.
10 Similarly, if you immerse infected mouse
11 brains in ethanol, another protein fixative, and then
12 autoclave, you get remarkable survival of infectivity
13 even though ethanol fixed in autoclave, 100 percent
14 recipient animals going down. So there is clear
15 evidence that if you fix the PrP protein by whatever
16 means, you, in fact, stabilize it to the extent that
17 it is not normally taken out by the standard
18 autoclaving procedures that we're looking at.
19 And to test the hypothesis a bit further,
20 we picked up on the experiments of David Asher's going
21 back, I think, to the 1980s. I think he was among the
22 first to observe that with scrapie-like agents, if the
23 materials are dried onto surfaces, they become
24 extremely difficult to inactivate.
25 Here, we have an infected brain homogenate

1 simply autoclaved and then injected into mice, and in
2 this case, one of the eight animals went down. If on
3 the other hand, we took the homogenate, dried it onto
4 a slide, autoclaved it and then reconstituted it,
5 scrape the top of the infectivity again and try to
6 challenge animals, 100 percent of these recipient
7 animals went down.
8 That, again, would be compatible with the
9 idea that this thin sheet of material on a microscope
10 slide in autoclave would be subject to very rapid and
11 efficient heat fixation. And there is one more
12 experiment that we carried out with this in mind where
13 we knew that dry heat at 160 for an hour would not
14 inactivate the agent, but that autoclaving without any
15 other processing was effective. We dry heated, which
16 would heat fix, and then autoclaved and, again, we had
17 substantially more survival of infectivity.
18 So my interpretation is that the effects
19 that we're seeing of smearing and drying of tissue in
20 tubes in autoclaving experiments may well be down to
21 heat fixation. I make no apology for the fact that
22 many of the experiments that I have done have used
23 brain macerate and not brain homogenate, that these
24 have all been more scarce conditions, because many
25 have been driven by public health concerns funded by

1 the Department of Health who do actually want to know
2 what happens under worst case circumstances that could
3 reflect conditions relating to tissues dried on
4 instruments, etcetera.
5 In terms of concern over instruments, the
6 Department of Health has funded quite a number of
7 studies relating to decontamination, disinfection.
8 They are quite interested in the combined hydroxide
9 and heating effect, and one of the concerns is what
10 effect does this have on stainless steel instruments
11 and devices?
12 So one of the studies being carried out in
13 Edinburgh is to look at test pieces made of stainless
14 steel before and after various hydroxide treatments.
15 It is mainly facilitated by collaboration with the
16 engineering department who have a scanning white light
17 interferometer where you can compare the roughness
18 indexes of surfaces before and after various
19 treatments. It will print out different graphs giving
20 you the roughness indexes.
21 And here, just to the naked eye are test
22 pieces, which on the left hand side are all untreated.
23 These are different grades of stainless steel. On the
24 right hand side are pieces that have been subjected to
25 autoclaving at 121 centigrade for 24 hours. And as

1 you can see, in some cases, there is hardly any
2 difference, but in some cases, there is a darkening of
3 the testing piece.
4 As I understand it, this is due to
5 precipitation of chromium salts and what I'm unaware
6 of is whether you can clean these chromium salts off
7 and start again with a pristine surface. This is what
8 was started before I left the unit, so I'm not quite
9 sure of the current state of play.
10 I will finish off with just three slides
11 containing anecdotal information, which may be of some
12 interest. One is that a low formalin fixed tissue is
13 incredibly difficult to inactivate, and one would
14 recourse usually to incineration for its disposal. We
15 did find that the hot hydroxide process, when applied
16 to infected brain tissue fixed in formalin was, in
17 fact, effective at removing that.
18 And I will finish up with two more
19 overheads, if I may. One goes back to the GME study,
20 and the figures may have changed slightly, but the
21 principles are nevertheless the same. It was
22 discussed how the superimposing of our sodium
23 hydroxide step, especially to the ossein material that
24 remains after the acidic extraction process where
25 there was a significant amount of infectivity

1 surviving, at that point. If you then applied -- I'm
2 sorry, this should be hydrochloric acid up here. If
3 you then apply .3 molar sodium hydroxide for two hours
4 at ambient temperature, there was no infectivity
5 detectable in the resulting gelatin.
6 This clearly suggests that earlier studies
7 using infected brain suggested that one more sodium
8 hydroxide is quite effective and not completely so,
9 these studies suggest that when you get the
10 circumstances in an environment such as ossein where
11 you are largely devoid of any extraneous lipids or
12 proteins, that the hydroxide process is much more
13 effective.
14 And I will leave you with some recent data
15 from a commercial study, which I have some sketch
16 information for you from. This involves a process
17 where raw materials exposed to saturated lime calcium
18 hydroxide, and then it goes on to hot lime at 80
19 degrees centigrade, here we are, sorry, and thereafter
20 onto even hotter lime at greater than 140 degrees
21 centigrade under pressure, much of the same conditions
22 if not higher conditions than those described that are
23 completely effective.
24 Now, the thing to be on your mind here is
25 that the pH of the lime, the maximum pH of lime is

1 significantly lower than that of one molar sodium
2 hydroxide. What we seem to be finding here is that
3 after the exposure to saturated lime for three hours
4 at 80, we do have some titre loss. The expectation
5 then might be that when you go on to this very high
6 pressure, high temperature process, that you might
7 lose all the infectivity, but, in fact, you do not.
8 To me, this demonstrates potentially two
9 things. One is that molarities of hydroxide lower
10 than one molar may not be truly effective under the
11 high pressure conditions and/or separately than any
12 surviving infectivity from this stage, which is
13 carried out at 80 degrees centigrade, the heat
14 fixation, which goes on in here, all the surviving
15 infectivity may, in fact, render it more resistant to
16 inactivation at this level. So these are speculative
17 comments, but they all contribute to the general
18 arguments about heat and hydroxide. And I will leave
19 it there. Thank you.
20 CHAIR PRIOLA: Are there any questions?
21 Oh, please, Dr. Edmiston.
22 DR. EDMISTON: I have a comment, which I
23 want to direct to the speakers, the previous speaker
24 and Dr. Taylor, and also a general comment to the
25 members of the panel in terms of how this applies to

1 surgical instruments in the operating room.
2 I am not surprised that you haven't
3 achieved complete inactivation, because as a rule,
4 it's a general trend we sort of adhere to, is as long
5 as there is biological material present or, I should
6 say, as long as the organic component is still there,
7 it's unlikely you're going to see complete
8 inactivation.
9 From a surgical perspective, one needs to
10 recognize, and I'm not quite clear on what my
11 colleagues are doing in Europe, but at least from the
12 U.S. perspective, we just don't take surgical
13 instruments and put them into an autoclave. There is
14 a pretreatment facility, which reduces organic
15 comment, and I know the next speakers will address
16 that probably in some detail.
17 Actually, I am heartened by some of the
18 data you have shown in terms of inactivation,
19 especially in the presence of high organic content.
20 The fact that in these high carbon environments, you
21 are able to reduce the number of viable particles, so
22 I think we need to think about this two step process
23 as we procedure through the next day and a half in
24 that we're just not talking about instruments being
25 directly sterilized. We're talking about a process in

1 which instruments are being rendered sterile by virtue
2 of not only a sterilization process itself, but also
3 the removal of organic material prior to
4 sterilization.
5 DR. TAYLOR: Yes. Could I make one
6 comment now? There is, at least in the UK, what I
7 consider to be a worrying trend, and that is that
8 traditionally in a very common sense fashion, it was
9 common in wards and even theaters for certain
10 instruments to be washed in the sink before they went
11 on for washing in the Central Sterilization
12 Department.
13 That process is increasingly being
14 discouraged for health and safety reasons. It's
15 resulting in an increasing number of instruments
16 reaching the Central Sterilization Department with
17 absolutely dried on blood, tissue and whatever, and
18 this is the problem that, I think, you are referring
19 to. The washing processes as they exist at the
20 moment, at least in the UK, are largely incapable of
21 dealing with the situation where you have material
22 that is absolutely dried or baked on.
23 DR. EDMISTON: And I think the
24 recommendations and this Committee needs to anticipate
25 the fact that that is a problem. Therefore, the

1 recommendations not only from this Committee, but from
2 other professional organizations such as APEC and
3 others would suggest that pretreatment of these
4 instruments is mandatory.
5 CHAIR PRIOLA: Yes, Bob?
6 DR. ROHWER: Yes. I am aware that that's
7 how it's done in the hospital setting. I work in a
8 hospital, but the problem that we have with that is
9 the potential for cross-contamination at the level of
10 the cleaning, and especially in a laboratory
11 environment at least, that would be a disaster for us
12 to spread this stuff around in our sinks and cleaning
13 stations before it ever got to the autoclave.
14 So we want to make absolutely sure that we
15 know that our instruments are contaminated. You don't
16 necessarily know that yours are, and so we want to
17 make absolutely sure that everything is gone before we
18 even handle them, and we do that by going to these
19 extreme measures.
20 On the other hand, the only thing that I
21 find encouraging about what you do is what standard
22 practice is in the hospital, is that slide that Dr.
23 Asher showed in his introduction. There really isn't
24 any evidence that instruments cleaned and sterilized
25 in the way that is specified by current practice are

1 causing CJD infections, and I think we have to give a
2 lot of weight to that.
3 On the other hand, I think it's also very
4 important to think about the cleaning step and what
5 kind of potential that poses for having a major
6 accident if you don't contain that particular
7 environment, as well, because I consider that a high-
8 risk environment.
9 DR. EDMISTON: Well, you need to know that
10 most of us have had a high threshold interest in this
11 for several years, and more and more of neurosurgical
12 instruments are being triaged and actually being
13 treated separately in separate kits. And for the most
14 part, and I will say for the most part, because there
15 are exceptions, are not getting into the main surgical
16 instrument stream.
17 And we're spending a lot of time and
18 effort with our neurosurgical colleagues to first of
19 all identify potential patients or suspected patients,
20 but overall, I can tell you most surgical departments,
21 most hospitals, will have unique surgical,
22 neurosurgical kits, and this is becoming more and more
23 common for the reason that you just mentioned.
24 DR. ROHWER: I guess the thing is I would
25 like to know more about how that segregation takes

1 place, because it's not particularly comforting to me
2 to know that the neurosurgical instruments are being
3 segregated. Neurosurgery is potentially the biggest
4 hazard in terms of passaging the disease, so you run
5 through a set of CJD exposed instruments, and then
6 that is followed by a set of cleaned instruments, you
7 know, coming from a normal patient or something like
8 that. How do you assure yourself that you're not
9 getting cross-contamination at the level of
10 neurosurgical instruments in that type of environment?
11 DR. EDMISTON: I won't go into a lot of
12 detail on this, because I know my colleague over here
13 will discuss it, but when patients are identified,
14 those instruments are quarantined and sequestered, so
15 that they are treated entirely separate from the rest
16 of the general instruments. So that is the policy
17 that most of us have developed over the years in
18 dealing with these suspected patients.
19 Now, the other issue is well, how about
20 all of the other neurosurgical patients, which you
21 find out about anecdotally? Now, that is an important
22 process to discuss, but in terms of those that we
23 identify or we suspect, those instruments are
24 quarantined and they are triaged and segregated out of
25 the system.

1 DR. ROHWER: Okay. Can I say anything
2 more? Are you tired of hearing me? I guess my
3 rebuttal to that would be that my guess is that the
4 greatest part of the risk comes from people that you
5 will never, ever identify as even carrying the
6 disease, and that's the greatest part of your
7 exposure. You will never know about it, and what I
8 see a need for is some way to actually effectively
9 sterilize the cleaning environment between uses.
10 CHAIR PRIOLA: Are there other questions
11 for the speakers? I have one quick one for Dr. Taylor
12 about the experiment you showed where you exposed
13 material to dry heat at 160 degrees, and you had
14 complete transmission. And then you took the
15 material, exposed it to dry heat and then, if I
16 remember, you autoclaved following the dry heat, and
17 that dropped to almost 50 percent survival or you get
18 50 percent survivors.
19 What implications do you think that has or
20 does it have any implications for multiple rounds of
21 autoclaving, say wet autoclaving or multiple rounds of
22 sterilization and getting rid of that residual
23 activity?
24 DR. TAYLOR: It's difficult to answer your
25 question within the context of infectivity dried onto

1 surfaces. All I can say is that I have done one
2 experiment where I didn't make any attempt to smear
3 and dry, but just using standard samples with the
4 hamster agent where after one round of sterilization,
5 and I am quoting figures very crudely here.
6 In the first round of a standard
7 autoclaving procedure, I lost something like 4 logs,
8 somewhere about there. And when that material was
9 taken and just reautoclaved, the loss on the second
10 round was about 1.7 logs. So the second autoclaving,
11 even under these conditions, was certainly not very
12 efficient, and I suspect would have been even poorer
13 if this had been agent that partially survived after
14 smearing and drying.
15 CHAIR PRIOLA: Dr. Gambetti?
16 BOARD MEMBER GAMBETTI: Listening to all
17 these presentations, of course, are very informative.
18 One, however, wish that experiments were available in
19 which decontamination of surgical instruments is
20 monitored under more realistic conditions. For
21 example, one wished that there would be some data on
22 decontamination of surgical instruments used
23 experimentally in a more surgical operation on a CJD
24 brain, and then see how this level of contamination
25 that is a classic level of contamination that you may

1 expect from a CJD brain in surgery, how the
2 decontamination is effective on those particular
3 conditions.
4 Vice versa, one would like to know how
5 much decontamination is achieved on contaminated
6 surgical instruments after the routine sterilization
7 that the surgical instruments undergo, as I said,
8 under routine conditions. Those are the data that I
9 would like to know whether they are available at all.
10 I have never seen, so I think those would be very
11 useful data to have for this discussion.
12 CHAIR PRIOLA: Dr. Taylor, do you have a
13 response to that?
14 DR. TAYLOR: Yes, I have an experiment
15 that I started before I retired, and I'm going to
16 throw the buck right over to Robert Somerville here as
17 my successor. In this experiment, the very question
18 that you're asking was asked. In other words, how
19 realistic or how appropriate are the inactivation
20 we're achieving to real life situations?
21 Now, we weren't doing neurosurgery on
22 human patients, but we were daily doing surgical
23 interventions within the brains of infected animals.
24 So we took deliberately infected instruments that had
25 been deliberately traumatized into animal brain,

1 subjected them to routine washing procedures, and then
2 proceeded to reuse these instruments again
3 neurosurgically or in subsequent animals.
4 My take on things before I left, and I
5 haven't looked at the data since, was that even the
6 washing processes in the lab, which were not anything
7 up to the Central Sterilization Department were having
8 a useful, if not complete effect. But by the time we
9 got to reuse of these instruments on animals, they
10 weren't, as measured at that time, producing any
11 significant levels of infections in the animals. I
12 don't know if Robert can add anything to these data or
13 are they still lying buried?
14 DR. SOMERVILLE: I think they are still
15 lying buried, David. I don't have access to the data
16 at present. What I would say to Professor Gambetti
17 though is that attempts, which I think Professor
18 Weissmann is addressing the Committee about tomorrow,
19 I think model the kind of situation that you are
20 trying to -- the kind of question that you're asking,
21 and that is the implantation of contaminated surgical
22 instruments, stainless steel. Professor Weissmann has
23 already done some studies with contaminated wares and
24 our lab is also hoping to initiate this kind of system
25 with different grades of stainless steel.

1 One of the problems that you have to
2 appreciate is that surgical instruments made out of
3 various kinds of stainless steel, and that is one of
4 the challenges of actually set up these kinds of
5 experiments, is how you model the different kinds of
6 surfaces that will be involved in real life. But to
7 summarize, I think the best way of testing your
8 question is through this kind of model.
9 CHAIR PRIOLA: Okay. I think we'll move
10 on to the next speaker who, as Dr. Asher mentioned,
11 was supposed to be Dr. Philippa Edwards, but she has
12 taken ill and is unable to attend, so Dr. Pedro
13 Piccardo from the FDA has graciously agreed at the
14 very last minute to give her presentation. Dr.
15 Piccardo?
16 DR. PICCARDO: Thank you. Well,
17 obviously, Dr. Edwards could not attend, and yesterday
18 I was given somehow the daunting task of presenting
19 the information that she provided. I will try to do
20 this as objectively as I can.
21 Next one. Okay. It has been settled
22 already iatrogenic transmission of Transmissible
23 Spongiform Encephalopathies from person to person has
24 occurred in non-Variant CJD, and this has instated
25 already, and here are the numbers that were provided

1 by a publication called Brown and Neurology in the
2 Year 2000. And as you see, the bulk goes to growth
3 hormone treatment and dura mater grafting.
4 However, there are here five cases
5 implicating which neurosurgery, meaning contaminated
6 instruments, have been implicated. On top of that, we
7 have a few cases following treatment with
8 gonadotrophin, chromium transplants and, of course,
9 electrodes here.
10 The next, please. However, one of the big
11 problems came when in 1986, Bovine Spongiform
12 Encephalopathy was described in the UK, and the
13 problem became humongous when in 1996, vCJD was
14 described in humans. As you see here, I mean,
15 obviously, there are a numbers of barriers that have
16 been established to try to prevent the transmission of
17 vCJD, the agent, from animals to humans. However, the
18 big question here is humans are being exposed. Humans
19 died with vCJD, and the question is we don't know how
20 many people has been exposed, how many people could be
21 infected.
22 The next one, please. And, of course, we
23 don't know how many people may be asymptomatic, at
24 this time and carriers.
25 The next one, please, the next one, the

1 next one. Okay. The next one, please. The next one,
2 please, the next one, the next one. So due to great
3 uncertainties, risk assessment has been considered.
4 What happened? Oh, okay. Here we go. Due to great
5 uncertainties, risk assessment has been considered.
6 The risk assessment has considered a wide range of
7 scenarios.
8 And why the risk assessment was done?
9 Basically, for two reasons. One was to determine the
10 risk of transmission of vCJD through surgical
11 instruments, and the second one to indicate what
12 measures could be the most effective to reduce the
13 risk.
14 The next one, please, the next one, next
15 one, next one, next one. The guidance follows the
16 assumption that an average of 10 milligrams of
17 material could remain in instruments, and this
18 information I gather from the document that was
19 provided by the CJD Incidence Panel.
20 Next one, please. Go ahead again, again.
21 The risk could be calculated for different scenarios,
22 and the effect of different actions could be
23 estimated.
24 Next, please. Next, please. Okay.
25 Improving the standards of decontamination is one of

1 the main objectives of the UK policy, and single-use
2 instruments have been considered, for example for
3 extraction of CSF, and the idea was to use as much as
4 possible single-use instruments without compromising
5 the clinical standards, of course. And a pilot
6 program was established to use single-use instruments
7 for tonsillectomies.
8 Next one, please. Go ahead. Why
9 tonsillectomies? Why was this chosen? Because
10 infectivity is present in vCJD in tonsils. I mean,
11 PrP has been found in tonsils from patients with vCJD.
12 The other thing was the relatively large number of
13 operations and the other thing is the young patients
14 usually with long life expectancy go through this type
15 of surgery, and these are instruments that can be
16 identified.
17 Next one, please. Okay. But there were
18 some adverse reactions. I mean, why there were
19 problems? One was you cannot probably think that the
20 problems raised from the quality of the sets, the
21 surgeon preferences and the other problems were
22 unrelated to the use of single-use instruments. So at
23 this time, there is an audit on this situation.
24 Next one, please. So what Dr. Edwards
25 tried to convey, the message that she tried to convey

1 with this cartoon is that while trying to solve one
2 problem, you create another.
3 The next one, please, again. The best
4 decontamination available cannot be guaranteed to
5 remove all sorts of infectivity, and single-use
6 instruments definitely is a situation that is not
7 possible for all kinds of surgery, so we must bear
8 that in mind.
9 Next one, please. Okay. Here, we have on
10 this panel, a tissue forceps, the tip of a forceps
11 that has been routinely decontaminated. Here, we have
12 electromicroscopy, and this what we can see here in
13 green is material that remains on the tip of that
14 forceps. This is the kind of material that remains.
15 This is florescent staining for protein, and this is
16 the superimposition of these two images gave this
17 image. So, obviously, there is a significant amount
18 of material that remains, a lot of which is protein
19 following routine decontamination.
20 The next one, please. So to reduce the
21 risk of transmission of TSE from person to person, the
22 Department of Health seek guidance from the Advisory
23 Committee.
24 Next, please. Next, please. And a first
25 version was done in 1998 and now, there is a revised

1 version, June 2003.

2 Next, please. This presentation

3 concentrates mainly on the risk arising from the care

4 of patients.

5 Next, please. Yes, okay. So well, one of

6 the issues is dealing with symptomatic patients. I

7 mean, when dealing with patients with CJD, there are

8 three types of definition. One is a definite case.

9 By definite we mean something that has been clinical

10 and pathologically confirmed. Probable case, which is

11 has clinical, but on top of that usually, there is

12 electron encephalographic analysis and there is MRI

13 imaging analysis, and possible CJD when usually is by

14 clinical presentation.

15 Next, please. Now, when we are dealing

16 with asymptomatic patients, when we talk about risk in

17 the case of -- when we talk about asymptomatic

18 patients and we talk about risk, we have to consider

19 two situations. One is in the case of inherited

20 diseases, and by inherited diseases, we consider that

21 there are two or more blood relatives are affected by

22 a prion disease or one or more blood relative showed

23 genetic testing, show a mutation in the prion protein

24 gene. Usually what is done is PCR sequence, the open

25 reading frame of the protein, and then from there you

1 can detect mutations.

2 Next, please. Now, the other is the

3 iatrogenic risk, and this case already was mentioned

4 treatment with hormones, dura mater grafts, and that

5 is why, I mean, obviously, the Department of Health

6 seeks advice.

7 Next, please. This table is based on what

8 we currently understand about the distribution of

9 infectivity in sporadic CJD or in non-Variant CJD, and

10 obviously, when we talk about tissue infectivity as it

11 has been said already many times, the highest amount

12 of infectivity is here in the CNS or retina and low

13 medium type of infectivity in the eye and olfactory

14 epithelium.

15 Next, please. Now, when we talk about

16 risk of different tissues in Variant CJD, the

17 situation varies, because we have to introduce into

18 the medium risk tissue lymphoid tissues. The rest

19 remains the same.

20 Next, please. So we don't have a problem

21 here and we don't have a problem here, because this is

22 by genetic testing or what was said already, is we can

23 know who these people are, and we understand who these

24 people are. But the problem is when we deal with

25 sporadic or when we deal with variant, people that are

1 asymptomatic, at this time, but might have
2 infectivity.
3 The next, please. Yes, okay. So the
4 problem comes or starts when, obviously, a CJD patient
5 is diagnosed, and immediately the question should be
6 has that patient had surgery or donated blood,
7 etcetera, and then try to assess what is the risk to
8 other patients that have been exposed to instruments
9 that have been used on this patient.
10 Next, please. And the risk, basically,
11 will depend on the type of tissue that we are talking
12 about, because we said already that there are tissues
13 with high levels of infectivity and in this case of
14 vCJD, the lymphoid tissue corresponds with tissues
15 with medium levels or medium risk.
16 Next, please. So this graph is an
17 estimate that comes from animal studies, so this is an
18 estimate that comes from animal studies. And,
19 obviously, the paren of tissue infectivity in vCJD
20 probably could follow this, and this is the onset of
21 clinical symptoms. So if we go, let's say that the
22 surgery was done way before the development of
23 clinical symptoms, probably the amount of infectivity
24 will be very low, and because we are dealing with vCJD
25 in this graph, we have two parameters or two tissues

1 to consider. One is the CNS and the other is lymphoid
2 tissues.
3 Next, please. So, as I said already, the
4 risk depends basically on the type of -- I mean,
5 depends once again on the type of tissue where the
6 surgery is performed, and if there is variable time
7 between surgery and onset of disease. Well, this
8 basically refers to the previous graph.
9 Next, please. Okay. One of the issues
10 here is that the risk depends -- let me see. In the
11 document provided by the CJD Incidence Panel, it is
12 stated that the first washing and autoclaving would
13 achieve at least a 105.4 reduction of infectivity, and
14 this was already mentioned by Dr. Taylor before, and
15 that subsequent cycles of decontamination reduce the
16 infectivity, but it's much less effective.
17 The next one, please. So at this time,
18 the Department of Health is in discussion with
19 manufacturers of surgical instruments. I mean, the
20 discussion is based on what is the probability of
21 using single-use instruments or to replace parts or to
22 provide instruments that could be easily
23 decontaminated.
24 Next, please. So what are the aims of the
25 CJD Incidence Panel? Well, it seems to be quite

1 obvious, which is to protect the patients. Let me
2 see.
3 Next, please. The aims. Go ahead again,
4 again. Next, please. No, yes, yes, here we go.
5 Obviously, the aims are to protect the patients and to
6 inform potentially exposed patients, and to inform the
7 public and to increase the knowledge.
8 Next, please. So in management of risk,
9 I mean, what is being done is quarantine the
10 instruments during the risk assessment, and
11 instruments that have undergone less than 10 cycles of
12 decontamination should be incinerated.
13 Next, please. Again, next, please. Okay.
14 So the patients will be contacted to alert them of
15 their possible exposure and to take health protective
16 actions. So these are the patients that should be
17 contacted under these circumstances. If the index
18 patient goes through, I mean, the material went
19 through high-risk procedures, the first six patients
20 that follow that first surgery should be contacted.
21 This is for tissues with less amounts of infectivity,
22 and these are the amount of patients that should be
23 contacted.
24 Next, please. So this is sort of the kind
25 of data that has been gathered during the last two

1 years of experience, and this is the incidence
2 reported to August of 2002, and definitely we have 39
3 cases implicated in Variant CJD, 39 cases implicated
4 in sporadic CJD, and that there are few that
5 correspond to familial or non CJD or unclear, cases
6 that could not be determined.
7 The next one, please. The type of surgery
8 is 131. So obviously, before were 87, I believe.
9 Yes, 87, and now, we are talking about 131 surgeries,
10 and the reason is that some patients went through more
11 than one surgical procedure. And what we see here is
12 that the GI surgery takes the bulk followed by
13 obstetric and gynecology and here we have neurology,
14 neurosurgery.
15 Next one, please. So in 76 incidents,
16 tracing was sought. Some or all were traceable, that
17 means in 34. In 18, it was not possible to trace
18 them. And in 24, there is incomplete information, at
19 this time.
20 The next one, please. So instruments that
21 have been quarantined are 48 and that have been not
22 quarantined are 39.
23 The next one, please. The fate of the
24 quarantined instruments, we have 21 that have been
25 returned to use, because it was assessed that the risk

1 was not higher than the usual risk for the UK
2 population. Here, we have four that have been
3 completely destroyed, the whole panel was destroyed,
4 because it was not possible to identify exactly which
5 of the instruments was involved. And in 23 cases, the
6 hospital directly decided to take care of the
7 instruments and destroy them.
8 The next one, please. So, obviously, this
9 is a very difficult task and there are a number of
10 dilemmas and difficulties, and there are a number of
11 scientific uncertainties, and it is very difficult to
12 trace back instruments and sometimes patients and, of
13 course, there are ethical issues that are involved.
14 The next one, please. Go ahead, yes. And
15 these are the websites that Dr. Edwards suggested
16 consulting for further information. I think this is
17 it. Thank you.
18 CHAIR PRIOLA: Dr. Khabbaz?
19 DR. PICCARDO: Oh, before -- excuse me,
20 sorry. Yesterday, after I learned that I had to give
21 this presentation, I called the UK immediately, right
22 away, and the first question I asked before you ask me
23 the question was what do I do with -- how do I handle
24 the questions?
25 So the thing is we will make clear note of

1 your questions, and then we will forward the questions
2 to the UK, and Dr. Edwards has been kind enough to
3 review them and, hopefully, if she feels well enough,
4 to provide the answer tomorrow. So we are in
5 business. Anyhow, if you want to ask the question, go
6 ahead.
7 CHAIR PRIOLA: So that gets you off the
8 hook, doesn't it, Pedro? Yes.
9 BOARD MEMBER KHABBAZ: You may know the
10 answer. I had actually a couple of questions. One
11 has to do with the adverse events related to single-
12 use of instruments for tonsillectomy. Do you have any
13 idea what types of adverse events would occur?
14 DR. PICCARDO: Yes, the answer is
15 bleeding, bleeding. That is the answer to that.
16 BOARD MEMBER KHABBAZ: Thanks. The second
17 question is I don't think -- I may not have understood
18 you correctly. I think when you talked about the
19 various types of CJD, you mentioned for inherited and
20 iatrogenic not concerned for infectivity?
21 DR. PICCARDO: Sorry, come again. I
22 mentioned --
23 BOARD MEMBER KHABBAZ: No infectivity for
24 inherited and iatrogenic versus sporadic and Variant
25 CJD. Is that in terms of how they got it or for

1 peripheral tissues?
2 DR. PICCARDO: Let me see. Can you pose
3 the question again? I have a problem hearing, too.
4 BOARD MEMBER KHABBAZ: Okay.
5 DR. PICCARDO: Listening to the question.
6 Yes, go ahead.
7 CHAIR PRIOLA: Yes. I think you're
8 referring to the slide you showed where you had
9 sporadic patients, iatrogenic and inheritable. And
10 are you asking if there was infectivity associated
11 with those patients?
12 BOARD MEMBER KHABBAZ: I didn't understand
13 the statement that there is no infectivity related to
14 inherited and iatrogenic.
15 CHAIR PRIOLA: Oh, I don't think that's
16 what you said.
17 DR. PICCARDO: No, well, I would be happy
18 to review Dr. Edwards' slide. However, my answer to
19 that is that there is no difference between inherited
20 and sporadic. We probably put them in the same box.
21 We will do a difference when we deal with Variant CJD,
22 because that is when we have tonsils and we have the
23 lymphoreticular system involved that we tend not to
24 have in sporadic or other forms of CJD.
25 CHAIR PRIOLA: Right, and I think that was

1 one to identify, patients at risk, right, prior to use
2 of instruments. If someone has inheritable mutation,
3 then that is a patient that you identify as being at
4 risk of possibly transmitting to somebody else. I
5 think that's what that --
6 DR. PICCARDO: Right, in terms of risk.
7 I mean, if you have a patient that, obviously, comes
8 from a family and has the mutation, etcetera,
9 etcetera, you know that patient is at risk already, so
10 it's very easy to recognize that patient. It's also
11 very easy to recognize a patient that, let me see,
12 that went through surgery that has a dura mater graft.
13 It could be a patient at risk. However, if you say
14 well, let's take sporadic CJD, maybe I am incubating
15 sporadic CJD and I don't know and no one will know.
16 CHAIR PRIOLA: Dr. Nelson?
17 DR. NELSON: How would you classify
18 cerebrospinal fluid that, let's say, has lymphocytes
19 or is an inflammatory cerebrospinal fluid? Would that
20 be the same as blood being low-risk or would it be
21 closer to CNS tissue?
22 DR. PICCARDO: Well, I would like someone
23 else, probably Dr. Asher, to attend that. Before we
24 go ahead with that, Dr. Edwards made clear that they
25 provide disposable instruments for CSF extractions, so

1 now, it's single-use. Go ahead.
2 DR. ASHER: Yes. In the NIH series, about
3 15 percent of spinal fluids from subjects with mostly
4 sporadic CJD did transmit disease to primates. So the
5 risk of spinal fluid is comparable to the risk of some
6 non CNS solid tissues, lymphoid tissue, liver, kidney,
7 spleen, lung.
8 DR. NELSON: But it's definitely higher
9 than blood?
10 DR. ASHER: Higher, definitely higher than
11 blood.
12 CHAIR PRIOLA: Yes, Dr. Gambetti?
13 BOARD MEMBER GAMBETTI: I believe that the
14 experiment that, David, you are quoting included not
15 only sporadic, but also Kuru patients, and three of 37
16 or so, spinal fluid tested transmitted the disease.
17 Do you know whether some of the CSF that transmitted
18 the disease were actually from Kuru patients, rather
19 than sporadic case? Do you know that?
20 DR. ASHER: I think it's in the '93
21 article, but I don't remember.
22 CHAIR PRIOLA: Okay. I think we'll move
23 on. Thank you, Dr. Piccardo. We'll move on to our
24 last speaker before the break if there are no other
25 questions, and that is Dr. Bill Rutala who is going to

1 discuss TSE agents and infection control in U.S.
2 hospitals.
3 DR. RUTALA: Thank you very much and good
4 afternoon. What I would like to do very quickly, and
5 certainly by looking at the next slide, review the
6 recommendations on and the practices in U.S hospitals
7 as it pertains to the prevention of cross transmission
8 from medical devices contaminated with prions and,
9 hopefully, have a few minutes to discuss how important
10 methodology is, and how important methodology is from
11 the standpoint that we can fail to inactivate even
12 easy to kill microorganisms like bacteria with FDA
13 cleared sterilization processes dependent upon the
14 methodology that is employed to include the absence of
15 cleaning.
16 Next slide. Let's begin with the
17 rationale for the U.S. recommendations, and these
18 recommendations have existed for decades, the
19 recommendations in infection control literature,
20 surgical literature, certainly, essential processing
21 literature and so forth.
22 But let's look at the next slide. As we
23 know as far as the epidemiology of prion transmission,
24 we know that it's not spread by contact. It is not
25 spread by airborne. It is not spread by environment,

1 but we are concerned about the iatrogenic spread.
2 Next slide. We can see here that
3 contaminated medical instruments have been implicated
4 in disease transmission, and we'll discuss that in
5 just a minute.
6 Next slide. Well, let's look at this
7 issue of prion transmission via surgical instruments.
8 Looking at the next slide, we see,
9 essentially, the two confirmed cases that have already
10 been mentioned. Those two confirmed cases, of course,
11 were reprocessed by a method that we never use in U.S.
12 hospitals, a combination of benzine, alcohol and
13 formaldehyde vapor, and then we also have four
14 suspected cases.
15 Those four suspected cases are involved
16 with CJD that has occurred in persons following brain
17 surgery. However, only one of the four had an index
18 CJD case identified. These cases occurred before 1980
19 and there has been no known failure of steam
20 sterilization to date.
21 Next slide. How about the infectivity of
22 human tissue as we discuss this rationale? As we
23 already know by looking at the next several slides, we
24 used epidemiology data and, of course, we used
25 experimental data and infectivity data. We know that

1 there is evidence of transmission via eye and brain
2 from an epidemiology standpoint, and we know that
3 experimentally we can inoculate animals, susceptible
4 animals, and demonstrate that certain body fluids and
5 tissues transmit CJD.
6 And we have already discussed the contents
7 of the next slide, which is that there are certain
8 tissues that are considered high-risk, certain tissues
9 are considered low-risk and, of course, some tissues
10 that are considered no risk.
11 Next, we see the issue of removing
12 microbes by cleaning, something that, certainly, we
13 need to discuss a little bit more as it pertains to
14 the methodology and how methodology is so important in
15 this issue of prion inactivation.
16 In the next slide, we will see,
17 essentially, something that has already been mentioned
18 by one of the panelists. The issue that effectiveness
19 should not consider only the effectiveness of the
20 disinfection of sterilization procedure, but also has
21 to consider the effectiveness of removal by cleaning.
22 And, of course, the probability of a device remaining
23 capable of transmitting disease is related to not only
24 the initial concentration of that prion on the
25 surgical instrument, but also it is related to the

1 effectiveness not only of disinfection and
2 sterilization, but also cleaning.
3 And there are literally dozens of studies
4 in the literature, which show how effective cleaning
5 is. Cleaning will reduce anywhere from 4 to 6 logs of
6 microorganisms by a manual or a mechanical cleaning
7 procedure. We don't have as much data regarding
8 protein reduction, but there are a few papers in the
9 literature that demonstrates there is, approximately,
10 a 2 log reduction of protein by the various cleaning
11 procedures.
12 In the next slide, we see the prion
13 inactivation studies. We don't need to go over this
14 very much. We're just going to very quickly go
15 through a few slides. We could possibly put a
16 question mark up here with prions. The question mark
17 I would put up there is related to the fact that maybe
18 the studies that have been done are artifactual in
19 nature and, essentially, a reflection of the
20 methodologies that are employed, and I think I can
21 show you data that would be supportive of that.
22 And then also, we would see here that
23 other microorganisms fall below possibly prions and
24 spores and it pertains to the susceptibility to
25 disinfection and sterilization procedures. And in

1 just a minute, I'm going to show you some data where
2 bacteria will survive FDA cleared sterilization
3 processes, because precleaning did not precede the
4 sterilization process.
5 Next slide. We know, of course, there are
6 many procedures that are ineffective or partially
7 effective.
8 Next slide. We know also that there are
9 some gaseous sterilization procedures and, of course,
10 physical procedures that are also ineffective or
11 partially effective processes.
12 Next slide. We can see, of course, that
13 there are some effective disinfectants and, of course,
14 by effective here, we're saying a 4 log reduction
15 decrease in the ID50 within one hour and, certainly,
16 among them include sodium hydroxide and sodium
17 hypochlorite.
18 The next slide will just tell us what the
19 effective processes are as it pertains to
20 sterilization, and this is what we use in U.S.
21 hospitals. We, of course, use sterilization primarily
22 by steam sterilization with a prevacuum sterilizer at
23 134 for 18 minutes. Sometimes, the combination of
24 sodium hydroxide and steam sterilization is employed,
25 but it's not widely employed because of some of the

1 deleterious issues associated with the combination of
2 sodium hydroxide and steam, deleterious, of course, to
3 the instruments, deleterious to the sterilizer and, of
4 course, the vaporization of sodium hydroxide to staff.
5 But we certainly recognize the effectiveness, and that
6 is an option for hospitals to choose.
7 Next slide. As it pertains to risk
8 associated with instruments, let's see what we have
9 with that.
10 Next slide. I just wanted to mention,
11 essentially, that there are certain categories of
12 instruments in every health care institution, not only
13 in the United States, but in the world. There are
14 certain instruments that we consider must be sterile.
15 They are instruments that have contact with sterile
16 tissue or the vascular system. We consider, of
17 course, then to be very critical.
18 There are other instruments like in
19 endoscopes that have contact with mucous membranes or
20 skin that is not intact, and we have a very high level
21 of disinfection associated with those instruments.
22 And the other instruments are noncritical, only have
23 contact with intact skin and, essentially, are not
24 involved in disease transmission.
25 The reason for mentioning that is seen in

1 the next slide and that is, essentially, in a minute
2 we're going to develop, essentially, the scheme for
3 how we disinfect and sterilize instruments in health
4 care setting in the United States.
5 As it pertains to surgical instruments, a
6 question was just asked. What is the microbial load
7 associated with surgical instruments? Actually, we do
8 know the microbial load associated with surgical
9 instruments. A few studies have actually evaluated
10 the microbial load. Of course, it's not for prions.
11 It's for other microorganisms, and microbial load 80
12 percent of the time is less than 100 organisms.
13 Rarely does it exceed 1,000 organisms. Many
14 surgeries, many different investigators have made that
15 observation.
16 Next slide. Well, this is how we decide
17 how to, essentially, employ special prion precautions
18 in U.S. hospitals. We, essentially, assess the
19 patient, assess the tissue and assess the device. Of
20 course, we consider whether it's a high-risk patient,
21 a high-risk tissue and a high-risk medical device,
22 again, those critical and semicritical devices.
23 Next slide. As far as that is concerned,
24 most U.S. hospitals then would do special prion
25 reprocessing, and that would be those higher

1 temperatures or a combination of sodium hydroxide with
2 steam, special prion reprocessing when it's a high-
3 risk tissue, a high-risk patient and a high-risk
4 medical device, and for all other situations with one
5 possible exception, it would just be conventional
6 disinfection and sterilization.
7 The one possible exception would be a
8 high-risk patient, a critical and semicritical device
9 and low-risk tissue. Some hospitals do treat low-risk
10 tissues from a high-risk patient, critical and
11 semicritical device as instruments requiring special
12 prion reprocessing, so possibly this would go into
13 that category.
14 Next slide. So the conclusions of this,
15 of course, is that from an epidemiology standpoint, we
16 have two cases of disease transmission that are
17 definitive, possibly four other cases. The guidelines
18 that we have discussed and are used in the U.S. are
19 based upon epidemiological evidence, tissue
20 infectivity, the risk of disease associated with
21 certain medical devices and, of course, inactivation
22 data, and the risk assessment is based again on
23 patient, tissue and device. And only when there is
24 critical and semicritical devices, contacting high-
25 risk tissue and possible low-risk tissue from high-

1 risk patients do we require, essentially, special
2 prion reprocessing.
3 Now, the next slide, we see, essentially,
4 what those special reprocessing procedures are. We
5 have already mentioned that this is the preferred
6 procedure that many hospitals use, the 134 at 18 and
7 a prevacuum sterilizer. There is no low temperature
8 sterilization technology that is recommended and we
9 know, essentially, that there are some disinfectants
10 that have activity against CJD.
11 Next slide. So this is what we're talking
12 about here. We're talking about used instruments, and
13 this is true for all used surgical instruments. They
14 are kept wet. They are not allowed to dry. They are,
15 essentially, cleaned before they are sent to central
16 processing. We don't let tissue and fluid dry on
17 them. When they get to central processing area, an
18 area where all instruments are received for a quality
19 control standpoint, the instruments generally go into
20 a mechanical washer disinfector. In the case of
21 special prion reprocessing, there would be a special
22 steam sterilization cycle, and that instrument would
23 be returned to health care.
24 Now, we have already mentioned,
25 essentially, the rationale. The last thing I want to

1 do is very quickly look at methodology and how
2 methodology affects results. And I am going to show
3 you some slides, and let's begin with the next slide
4 where, essentially, we can fail to kill easy to kill
5 microorganisms by methodological manipulations, and I
6 will call them manipulations, because all we do is we
7 don't add cleaning to, essentially, the process. And,
8 of course, we have already seen how important cleaning
9 is.
10 Next slide. This is the issue. I don't
11 want to get too involved in this, but, essentially,
12 the point needs to be made that there are a number of
13 studies that have been done, and most of those studies
14 are done in a worst case scenario, of course, and, of
15 course, we try to achieve sterilization by using
16 appropriate reprocessing procedures.
17 And there are no studies, including the
18 studies that have been published involving cleaning,
19 that reflect the reprocessing procedures in a clinical
20 setting. We use enzymatic cleaners. We use
21 mechanical sterilizers in a closed system and we use
22 mechanical washer disinfectors in a closed system.
23 Next slide. Now, I want to talk briefly
24 how factors affected sterilization, and many factors
25 affect sterilization, but I am only going to choose a

1 couple. First, let's look at protein and salt.
2 Next slide. If we just put, essentially,
3 some microorganisms on a penicylinder like this right
4 here, next slide, and then we let it dry for 30
5 minutes, next slide, and then we put those
6 penicylinders that are inoculated with easy to kill
7 microorganisms, such as E. coli and pseudomonas and
8 enterococcus faecalis in a FDA cleared sterilization
9 process like ethylene oxide or hydrogen peroxide gas
10 plasma, in the absence of serum or salt, you get 100
11 percent kill.
12 In the presence of serum or salt, you get
13 40 percent failure, as well as in this case, 63
14 percent failure, a significant amount of failure,
15 because cleaning did not precede the sterilization
16 procedure. Now, the amount of salt and serum is not
17 really that high. The amount of salt is .65 percent.
18 The amount of serum is 10 percent, but failure in the
19 absence of any cleaning.
20 Next slide. If we use, essentially, a
21 lumen device and do the same experiment, next slide,
22 we see, essentially, 60 percent failure. Again, we're
23 failing to sterilize instruments that are contaminated
24 with easy to kill microorganisms, because we failed to
25 clean them. And it's not really the lumen device that

1 is causing the problem, because we see here in the
2 absence of serum or salt, those organisms are killed.
3 So the failure to clean allows the survival of easy to
4 kill microorganisms in a sterilization process, such
5 as low temperature sterilization.
6 Next slide. So all technologies have
7 limitations. Salt and serum provide protections for
8 spores and bacteria, and salt and serum with a lumen
9 carrier even provides extraordinary protection.
10 Next slide. Now, let's look at the issue
11 of cleaning and let's look at spores.
12 Next slide. Let's just put some spores on
13 a stainless steel scalpel and we'll see on the next
14 slide. We're going to put about 106 geobacillus
15 stearothermophilus spores on this stainless steel
16 scalpel, and then we're going to put that scalpel in
17 a low temperature sterilization technology, such as
18 hydrogen peroxide, gas plasma in the absence of
19 cleaning, and we can see complete failure here. 60
20 out of 60 positive stainless steel scalpels.
21 Now, let's look at the next slide where
22 the only thing we did is we again put the spores on
23 the stainless steel scalpel.
24 And then the next slide. All we did was
25 place the stainless steel scalpel into either

1 distilled or tap water for 60 seconds, just placing it
2 there for 60 seconds, taking it out and then putting
3 it into low temperature sterilization technology.
4 Next slide. You can see that there is
5 complete success, a complete ability to kill
6 microorganisms to include spores just because of a
7 static soak. Of course, you can see here a very light
8 rinse also was successful.
9 Next slide. Here, we are going to,
10 essentially, try to identify why this is happening,
11 and what we're really looking at is what is going on
12 as far as chloride, protein and spore concentration by
13 just doing that static soak.
14 In the next slide, we see, essentially, in
15 a matter of seconds we see the salt, protein and
16 spores released from the fetal bovine serum dried on
17 stainless steel blades and placed into deionized water
18 at room temperature. In a matter of seconds,
19 essentially, you get significant reductions in salt,
20 proteins and spores.
21 Next slide. Now, so what we found is,
22 essentially, inorganic, organic and microbial
23 contaminants on the device are dramatically reduced
24 during washing and, of course, there is a significant
25 reduction of spores.

1 Next slide. Well, let's see if that is
2 effective for steam sterilization. Right now, we're
3 really talking about these low temperature
4 sterilization technologies. Does the same thing
5 happen with steam sterilization? This is a study from
6 Doyle and Ernst in 1967 where, essentially, all they
7 did was monitor the effect of spore occlusion and
8 calcium carbonate crystals in inactivation in steam
9 dry heat and ethylene oxide sterilization processes.
10 They were just inoculating 103 or 8 times
11 103, bacillus subtilis spores, and let's see what
12 happened because of the spore occlusion and calcium
13 carbonate. Here, we see steam at 121 degree
14 centigrade in the unoccluded spores, the biological
15 challenge. It only takes 10 seconds. You can kill
16 104 in 10 seconds, no time. But in the presence of
17 the calcium carbonate, to kill that 104 took 150
18 minutes. For dry heat, it's three and a half hours.
19 In the presence of the calcium carbonate, it's 50
20 hours.
21 Next slide. So, essentially, a number of
22 things have been found, that is contact with water or
23 cleaning for just a short period of time rapidly leads
24 to the dissolution of crystals, of course, removed
25 microorganisms and, of course, also has an effect on

1 protein elimination. And, of course, minimal cleaning
2 eliminates the effects of these salts, which effect
3 the effectiveness of sterilization processes. And
4 simulated use tests that do not include washing would
5 not represent conditions that exist in clinical use
6 situations.
7 Next slide. And this is, essentially,
8 what you see in electron micrograph. If you look at,
9 essentially, .75 sodium chloride in the presence of
10 spores, you see the salt crystal, essentially,
11 occluding the microorganisms from exposure and,
12 essentially, cleaning dramatically effected those
13 results.
14 Next slide. The point that we need to
15 make for all these studies that have involved prion
16 inactivation is that you can clean without
17 sterilization, but you never can sterilize without
18 cleaning. That is a point, a principle, that is known
19 to every professional in health care, certainly, every
20 professional that is involved in reprocessing
21 instruments.
22 Next slide. So the conclusions would be
23 all sterilization processes are effective in killing
24 spores. Salts favor crystal formation and impairs
25 sterilization not only for low temperature

1 sterilization, but also high temperature
2 sterilization. Cleaning removes salts and proteins
3 and must precede sterilization. Failure to clean or
4 ensure exposure of microorganisms to the sterilant
5 could affect the effectiveness of the sterilization
6 process. We say repeatedly if the organism does not
7 have exposure to the germicide or the sterilant,
8 inactivation will not occur. And, of course, these
9 salts and protein materials and possibly other
10 environmental conditions to include surfaces affect
11 that exposure. And lastly, CJD inactivation studies
12 should be consistent with actual clinical practice.
13 I think we have done what we said we were
14 going to do. We have looked at the recommendations
15 from the U.S. We have talked a little bit about
16 methodology and how methodology affects results not
17 only for hard to kill organisms such as spores, but
18 easy to kill microorganisms such as bacteria.
19 Next slide. I thank you very much for
20 your attention.
21 CHAIR PRIOLA: Okay. Thank you, Dr.
22 Rutala. Are there are questions from the Committee or
23 from Dr. Taylor? Would you like to make a comment?
24 DR. TAYLOR: Just a couple of quick
25 comments. A very nice talk and very much to the

1 point, I think. Two comments, one is mentioned that
2 generally, the washing procedure is usually pretty
3 effective in taking off bacteria and spores, etcetera.
4 The one comment here is that one might anticipate that
5 TSE infectivity might, nevertheless, be somewhat more
6 adherent to instruments because of the hydrophobicity
7 of the PrP protein.
8 The other comment is that there are
9 concerns about damaged autoclaves by hydroxide, but
10 that is certainly not inevitable, because it depends
11 on the grade. The commercial company that we asked
12 where do you dispose of animal carcasses, in reactor
13 vessels with hot hydroxide, have had vessels running
14 for many years now and they have certainly subjected
15 these to x-ray analysis, etcetera, and they are
16 absolutely fine.
17 DR. RUTALA: To your two points, I
18 certainly agree with the first point. Certainly, the
19 data that I presented, of course, are non-prion
20 proteins, as well as microorganisms and, certainly,
21 the same type of analysis needs to be done with prion
22 proteins, and I support that work.
23 In regard to the second point, the effect
24 of sodium hydroxide on sterilizers, certainly some
25 sterilizer manufacturers have threatened the owner of

1 the sterilizer that in the hospital, if they use
2 sodium hydroxide in the sterilizer, they will nullify
3 the warranty, which, of course, affects the
4 utilization of sodium hydroxide.
5 But there are ways, as you probably know
6 better than I do, to limit that vaporization and
7 contain the vaporization with, for example, containers
8 that have lids. And certainly, Dr. Asher knows more
9 about that, and possibly that can be discussed.
10 CHAIR PRIOLA: I have one very quick
11 question before Dr. Rohwer makes a comment, and that
12 is you stress very strongly that instruments are
13 always kept wet, so that you don't have this problem
14 of material drying on the instrument and then perhaps
15 adversely affecting its ability to be sterilized.
16 During a surgery -- I mean, I know that
17 when I do my little surgeries on mice that as you're
18 doing it, stuff does dry on the instrument just as
19 you're poking around, so how is that dealt with?
20 DR. RUTALA: Well, many times -- it is
21 dealt with in different ways. Many hospitals,
22 essentially, don't even take the surgical instrument
23 and put it on a dry tray. They very commonly place it
24 in a basin, which has, for example, saline or water or
25 possibly even a germicidal agent, so it doesn't go

1 into a setting, which is going to allow dry fluids and
2 tissues to be achieved.
3 And then, of course, the other issue is
4 that there is sometimes precleaning before it is sent
5 to central processing. Central processing does not
6 want instruments that are contaminated with tissue and
7 blood. They won't accept instruments that are
8 contaminated with tissue and blood. Sometimes, there
9 is also a washer sterilizer that, essentially, is a
10 precleaning procedure before it goes to central
11 sterilization.
12 So different hospitals do different
13 things, but the one thing in common is there is an
14 effort to keep it wet, and there is an effort to keep
15 it clean, because most central processing areas won't
16 accept surgical instruments that have dried tissue on
17 them or bloody instruments.
18 CHAIR PRIOLA: You know, I understand
19 that. I guess my point was more during the procedure
20 as you use the instrument. Just as you're using it,
21 it's going to air dry, because it is exposed to the
22 environment, and so you can't keep it wet the entire
23 time. I mean, you're just going to have some dried
24 material that will probably be taken care of possibly
25 by the cleaning and whatnot.

1 DR. RUTALA: Yes.
2 CHAIR PRIOLA: But some drying will occur
3 no matter what you do.
4 DR. RUTALA: And by immersion in the bath,
5 but some drying, depending upon the level, of course,
6 will occur.
7 CHAIR PRIOLA: Okay. Dr. Rohwer, what was
8 your comment?
9 DR. ROHWER: Yes, I have a couple of
10 comments and also would like to get Dr. Rutala's
11 opinion on something, and that is first, I would
12 highly advise not autoclaving with the lid on the
13 vessel, and I am also mystified by this concern about
14 sodium hydroxide vapors. As far as I know, sodium
15 hydroxide has no measurable vapor pressure, and a
16 properly operating autoclave should not be
17 aerosolizing it either, because it shouldn't boil on
18 the way down. That is my first point.
19 But what I would like to have you address
20 is this issue of cross-contamination at the level of
21 washing, because that is our major objection with that
22 approach. We're talking about an agent that is very
23 difficult to get rid of. If it gets spread around the
24 laboratory and the environment then, we just couldn't
25 tolerate that. You know, we don't want it in our

1 sinks. We don't want it on our surfaces, etcetera.
2 And so how is it that you deal with the
3 eluates and the washers that come off of a set of
4 instruments, which you know have been exposed to a
5 Creutzfeldt-Jakob Disease patient, for example? How
6 are the washers sterilized? How do you dispose of
7 that?
8 It seems to me you create a cascading
9 level of problems that have to be dealt with, and I am
10 absolutely willing to concede all the points that you
11 are making, except that in the case of this particular
12 agent, it is very difficult for me to accommodate this
13 idea of spreading this stuff around, exposing myself
14 to it willingly before it has actually been
15 decontaminated.
16 DR. RUTALA: Well, to your point,
17 certainly, this practice has been employed for a
18 number of years, and I think it has been practiced for
19 the following reasons. One, of course, in a
20 decontamination area in central processing, the
21 persons in that area wear personal protective
22 equipment. They wear gowns, gloves, protective masks.
23 Second is that nearly every hospital where
24 decontamination takes place in central processing,
25 it's a closed unit. It's a washer disinfector

1 completely closed. That is there is no aerosolization
2 of droplets, of fluid that are related to the washing
3 procedure. It's a closed procedure.
4 The closed procedure, of course, has many
5 steps to it. Some of them are the use of enzymatic
6 detergents, high temperatures, rinses and so forth.
7 And I guess the third point related to that,
8 protective apparel, a closed system, is the issue that
9 while there is a recognition that some prion proteins
10 may go down the drain connected to a sanitary sewer,
11 we don't believe that that's the only source of prions
12 reaching, essentially, the sanitary sewer system.
13 And to that point also, prions, of course,
14 are unlike many other infectious diseases, are not
15 transmitted by direct contact, indirect contact,
16 droplets spread, airborne or the environment. So I am
17 not sure what the level of concern is as far as
18 transmission. It certainly wouldn't be, as I look at
19 the issue, transmission to health care workers, it
20 could possibly be contamination of the environment,
21 but I believe that there is other forms of
22 contamination in the environment outside that setting.
23 CHAIR PRIOLA: Dr. Bailar?
24 BOARD MEMBER BAILAR: Very nice talk. I
25 do have a question about this very simple

1 straightforward slide you had on the decreasing order
2 of resistance of microorganisms disinfected in
3 sterilants. You didn't go into the details of that,
4 but I suspect it's ranked on the basis of things we
5 know are effective at the susceptible end, that is the
6 bacteria and the enveloped viruses.
7 Is anybody looking at other kinds of
8 agents, you might call them unconventional agents,
9 that may not be very effective at that end, but might
10 be pretty good with prions?
11 DR. RUTALA: As far as that slide is
12 concerned, you know, it is a general slide. There is
13 an exception to that slide as it pertains to
14 germicidal agents and particular groups of
15 microorganisms, but it is a general slide. As your
16 question intimates, most of the data, and there is
17 literally hundreds of papers that support that slide,
18 and most of the data is with the types of germicides
19 that you have seen today and in my presentation and in
20 other presentations. That is the conventional, not
21 the nonconventional germicides and sterilization
22 processes, products such as the alcohols, the phenols,
23 the ethylene oxide, the steam sterilization and dry
24 heat and so forth. Does that answer your question?
25 BOARD MEMBER BAILAR: Yes, it leaves me

1 wondering whether it might be worthwhile for somebody
2 to try some of these things, but I am no expert in
3 this field.
4 DR. RUTALA: Well, to your point, I think
5 that there are people interested in that.
6 CHAIR PRIOLA: If there are no more
7 questions, we have two more speakers, but I think we
8 should take maybe a 10 minute break. We're about 15
9 minutes behind, but let's take a 10 minute break and
10 reconvene at 5:10.
11 (Whereupon, at 5:06 p.m. a recess until
12 5:18 p.m.)
13 CHAIR PRIOLA: If I could have the
14 Committee members take their seats, so we can conclude
15 this session. Okay. Our next speaker is Captain
16 Edward Rau, Environmental Health Officer for NIH, and
17 he is going to discuss infectivity of air emissions
18 and the incineration of scrapie tissue.
19 CAPTAIN RAU: Thank you very much.
20 Unfortunately, our only TSE expert in our group, Paul
21 Brown, couldn't be here today. He is on some kind of
22 a hardship assignment in southern France at the beach
23 right now, so he has left that up to me to take care
24 of.
25 The other disclaimer is that the results

1 that I am going to present here are really very
2 preliminary. Our experiments are still in progress.
3 The paper is not written. None of the data is
4 published. So with that, we'll go ahead here.
5 Could I have the next slide, please? I
6 don't need to elaborate on all of the difficulties
7 there are in inactivating the prion agents, and that
8 the resistance to thermal inactivation is, of course,
9 highest under conditions of dry heating. And that has
10 led some concerns about even incineration being an
11 effective technology to dispose of certain TSE waste.
12 Sitting here this afternoon, I think I
13 have a new definition for incineration. It's that
14 process, which incorporates all of the things that
15 make inactivation difficult to do. We start out with
16 a material that has been smeared and mashed around by
17 all the handling of the medical waste process. It has
18 not been precleaned. In fact, it is, in some cases,
19 pure dirt. Then we're going to take that into a
20 process, which begins by a drying and probably
21 fixation step, and maybe melt a few varnish like
22 materials over it before we really get into the
23 combustion process.
24 Next slide, please. As you are aware,
25 incineration is still the technology of choice for

1 disposing of most medical waste that contain TSEs, and
2 it is also being used to dispose of large volumes of
3 animal products, contaminated carcasses and so forth,
4 some of which are still in large quantities in
5 storage. The potential for TSEs being in emissions
6 from combustion processes is of public concern, and
7 has received very little investigation so far.
8 Next slide, please. We have published
9 some previous experiments documenting the
10 unprecedented level of resistance to thermal
11 inactivation, both crude brain tissue and purified PrP
12 from the 263 scrapie infected hamsters. That included
13 a partial inactivation after heating for 300 degrees
14 for 15 minutes, and several transmissions after
15 actually ashing brain material at 600 degrees C. And
16 at those higher temperatures, there were similar
17 patterns of resistance in both formalin fixed and non-
18 fixed tissues.
19 Next. The objectives of our experiments
20 in progress are first to confirm the results from our
21 previous study. Some people were a little bit
22 skeptical about the transmission after 600 degrees C.
23 Others might have even labeled it science fiction.
24 And secondly, we wanted to investigate the potential
25 for transmission via the air emission that might come

1 from a medical waste incinerator.
2 Our previous experiments were rather
3 primitive in that we merely headed brain tissue
4 macerate in vented crucibles. The new experiments, we
5 are actually going to simulate the conditions of
6 humidity and the gas mixtures and so forth that occur
7 in two types of incinerators.
8 The first are the reducing environment or
9 starved air incinerators. These are the most commonly
10 used type of incinerator in the United States. A
11 synonym for that is the controlled air incinerator.
12 The other situation we wanted to look at was an
13 oxidizing environment or referred to as a normal or
14 excess air incinerator. And in this study, we
15 repeated the temperatures that were used in the
16 previous study, 600 degrees and 1,000 degrees C.
17 Next. Materials, our tissues samples were
18 cooled, hamster brain tissue macerates from terminal
19 animals with the 263 scrapie strain, about 10 logs of
20 infectivity per gram, and for controls we had tissue
21 from normal animals. The incineration situation was
22 referred to as a Lindberg Furnace in a quartz reactor
23 tube, the removal of the specimen crucible and holder.
24 The gas supply coming into the incineration unit was
25 normal air or nitrogen with flow and humidity

1 controls. And then coming out of the unit was an
2 impinger train and terminal filter for collection of
3 the air emissions.
4 Next slide. This is a photograph of the
5 main part of the simulator. It all fit in a large
6 chemical fume hood. The incoming gases come into the
7 furnace here. The quartz tube is contained inside of
8 the Lindberg Furnace. This is a pyrometer. And then
9 the outflow coming out of the combustion process goes
10 into this impinger system, a series of collectors, the
11 first one being ice water bath. The second one, dry
12 ice, and then out through a terminal filter.
13 Next. This schematic gives an idea of the
14 inside of the reactor tube, inside of the furnace.
15 The tube is, approximately, one inch diameter, all
16 quartz construction. At this end, we can remove the
17 plug and insert into a thermocouple to directly
18 measure the temperature or we can insert the sample on
19 a glass rod, which is housed right here.
20 The gas flow comes from this direction in
21 the top. It passes the sample. Exists through a ball
22 joint and then on to the impinger train. In designing
23 this, we tried to ensure that all the components in
24 the system were inert. We used quartz and teflon
25 joints as the materials.

1 Next. This schematic shows a little bit
2 more information about the impinger system. It's a
3 rather challenging design, because we really didn't
4 know what we were trying to trap coming out of this
5 process. Again, we have the ice water bath and the
6 crushed dry ice bath following into a cartridge filter
7 and exhausting into the hood.
8 Next. The methods began by introducing a
9 one gram sample of the brain tissue into the reactor
10 tube. We incinerated that for 15 minutes at either
11 600 or 1,000 degrees in either normal air or starved
12 air conditions. Following the process, we collected
13 the air and air emission samples separately from each
14 run, and then replaced the impinger train between each
15 run. We didn't have enough reactor tubes to use one
16 for each experiment, so we disinfected those with
17 bleach after each test.
18 Next. So each experimental run gave us
19 three different samples. We had the ash residue that
20 was collected in the crucible. The small amount of
21 residue that formed in the reactor tubing as it exited
22 the quartz reactor and came out cooled down at the
23 border of the furnace, and then the emissions
24 collected in the impinger traps.
25 Next. This gives you the array of samples

1 that we collected. We ran both normal and infected
2 tissues in the two different gases, two different
3 temperatures, and for the infected material, that gave
4 us three different samples. We combined samples for
5 two of the normals and we did not run some of the exit
6 tubes and traps on those. The reason for that is
7 simply economics. We're dealing with about 500
8 animals to be maintained here, a great cost and time.
9 Next slide, please. The bioassay method,
10 we concentrated the samples of the ash and emissions
11 from each test into, approximately, a one milliliter
12 volume in saline, and that was intracerebrally
13 injected into, approximately, 30 Wingling hamsters.
14 That is about 3 hundredths of a milliliter per animal.
15 So the entire emission from each test was injected.
16 We're not taking a sub sample out of those emissions.
17 The entire emission from each burn was injected into
18 animals.
19 Animals, of course, were segregated by
20 test group. We observed them over 12 months for
21 symptoms and then examined all of the brains for the
22 presence of prion proteins by Western Blot testing.
23 That testing is still in progress on the negative
24 appearing animals.
25 Next. Results, we had no transmissions

1 from the controls. There was some possibility, my
2 commentor thought, we might be able to get some kind
3 of symptoms as artifacts of this trauma and injecting
4 into the animals, this residue. We just wanted to
5 rule that out. We had no transmissions from any of
6 the materials collected at the 1,000 degree C burn,
7 and we had no positives from any of the residues
8 collected in the impingers or the end of the reactor
9 tube.
10 However, we did get two transmissions, and
11 these were after very long incubation time from the
12 ash from the crucible from the 600 degree group in
13 normal air. The asymptomatic animals, again, we're
14 still testing those for silent infections. We're not
15 finished with that, so we have to call our results
16 preliminary, at this point.
17 Next. Conclusions from the experiment.
18 First, that the results were very similar from the
19 previous study showing that there is, apparently, a
20 threshold transmission from tissues at about 600
21 degrees C. The low transmission rate and very long
22 onset time for the symptoms suggest, again, that that
23 is the extinction temperature or very near it. We
24 found no evidence of infectivity in the air emission
25 samples.

1 Next. Speculate a little bit about what
2 the environmental implications of this are. First, we
3 did not see any evidence of transmission in the air
4 emissions, so it's probably unlikely that will have a
5 possible emission to the air from a properly operated
6 medical waste incinerator. It is possible that some
7 survival of the agent could occur in ash if there is
8 not enough penetration of the temperature and time of
9 exposure in the ash bed.
10 I wanted to kind of put this in
11 perspective a little bit though, because I think it's
12 a very low potential for transmission. First off, as
13 Dr. Taylor said, we don't see environmental sources in
14 transmission going on. Secondly, what we are seeing
15 these two positives on is a simulated burn load that
16 is pure material with 10 logs of infectivity per gram,
17 and we're collecting virtually of the residue from
18 that and injecting it into, approximately, 100
19 animals. So there is a very low level of infectivity
20 in that material that is coming out.
21 Probability of survival in ash not only
22 depends on a lot of factors, the load density, the
23 turbulence, the type of equipment, other operational
24 factors. And as we heard earlier today about the
25 importance of context, I really can't imagine a more

1 complicated context than a medical waste incinerator
2 and all the combustion and mixing and reactions and
3 things that are going on inside of that process.
4 Next. Our colleagues at EPA felt that
5 these factors probably would be the most important in
6 increasing the potential for prion survival in ash
7 from medical waste incinerators. Under normal
8 conditions, there are certain design factors,
9 particularly in the grate oriented designs that might
10 allow some of the material to not be treated for 15
11 minutes. It falls through the grates or it somehow
12 gets passed on through the system faster than the
13 nominal residence time for the solids.
14 Particularly, as things are just inserted
15 into the incinerator, you tend to get a boil off of
16 some of the material, a flash burn. That can be
17 carried over very quickly into the second chamber.
18 The other factor is that the ash bed temperatures
19 often may run 100 degrees C lower than the actual air
20 temperature.
21 Reported temperatures for incinerators
22 refer to the air. That is what is being monitored,
23 and not the actual temperature in the ash. Under
24 abnormal conditions, a lot of things can really go
25 wrong, cold start up conditions, overloading,

1 inadequate control of the under fire air flow.
2 Next. We tried to compare what our
3 experimental conditions were with the conditions in
4 actual medical waste incinerators and some other types
5 of processors used for bone meal products, and the
6 most common incinerator in the U.S., the controlled
7 air or starved air type of incinerator, in that
8 primary chamber, you have temperatures of about 760 to
9 980. If you subtract about 100 degrees from that,
10 allowing for some cooler temperatures in the ash,
11 we're right on that threshold of survival that we saw
12 in our experiments.
13 The secondary chamber, which mostly sees
14 the pyrolysis products and not the ash is usually well
15 up into that 1,000 degree temperature. I don't have
16 much information on the temperatures in the excess air
17 incinerators. They are probably quite variable
18 because of the way that process is run. The secondary
19 chamber is, again, quite hot, sufficient probably to
20 inactivate prions.
21 There is some information on the other
22 types of burn units that are being used in Europe for
23 disposal of the meat by-product material. One of the
24 articles had indication that there is actually a
25 measurement of temperature at the ash grate in this

1 800 to 1,000 degree range, which looks pretty good for
2 inactivation.
3 Next. There are other possible
4 incineration options. If we get into a situation
5 where we have a large amount of material to dispose
6 of, the mass burn municipal waste incinerator in the
7 United States operates at about 1,000 degrees, so that
8 would likely inactivate prions.
9 Western Europe is looking at a variety of
10 other types of industrial incinerators, fuel burners
11 and so forth. Again, they have some high temperature
12 and residence times. In one system, a holding time of
13 30 to 40 minutes, which is very encouraging.
14 I think that's the last slide. Next. I
15 believe that is the last slide. Again, our results
16 are very preliminary. So far, all of the testing on
17 the negative appearing animals is confirming that's
18 the case, but we're not quite finished with that yet.
19 Any questions?
20 CHAIR PRIOLA: Any questions from the
21 Committee? All right. Thank you very much, Captain
22 Rau.
23 CAPTAIN RAU: Thank you.
24 CHAIR PRIOLA: Our final talk of the --
25 oh, I'm sorry. You had a question? Oh, sorry. Yes,

1 go ahead.
2 DR. ROHWER: One issue I had with the
3 original study was that the thermocouples were not
4 actually in the sample, and the sample was loaded wet,
5 and it wasn't clear here whether you're starting with
6 wet tissue or dry tissue, and where the temperature
7 measurement is actually being made, vis-a-vis, the
8 sample. And the reason I bring this up is that a wet
9 sample will not spend as much time at 600 degrees as
10 a dry one, because you got to boil off the water
11 first, and that could actually take some time.
12 CAPTAIN RAU: We did start with wet
13 samples, wet tissue samples. The burn time is 15
14 minutes, however, in here, so I think we're probably
15 spending most of that time at temperature. With
16 regard to the thermocouple, before each sample was
17 inserted, it was measured, then the thermocouple was
18 withdrawn. We still have a pyrometer on the outside
19 of the tube that we're confirming temperatures with,
20 and that is really the best we could do. There is
21 just not a way to have the thermocouple in there and
22 be able to insert and withdraw a sample out of there.
23 I agree with your boil off concern, but that is also
24 real world, what's happening in the incinerator.
25 DR. ROHWER: In the original experiment,

1 there was a thermocouple between the crucibles, so I
2 took that to mean that there are thermocouples that
3 can survive those kinds of temperatures. Is that
4 incorrect?
5 CAPTAIN RAU: Yes, the problem is getting
6 the output out of the burn chamber. It was a design
7 issue. But in the first experiment, the thermocouple
8 was right adjacent to the crucible and we were able to
9 measure that in the muffle furnace.
10 CHAIR PRIOLA: Okay. Thank you. I think
11 we'll move on to our last speaker who is Dr. David
12 Asher from the FDA, as well as Dr. Brown, Dr. Stanley
13 Brown. Oh, actually, you're going to start.
14 DR. BROWN: Actually, the last team is --
15 I am the rigger coming in from CDRH. Could I have my
16 first slide, because it tells the whole story? Let's
17 see, it worked on my computer. It was created on
18 Terry's computer.
19 Well, anyway, I'll start. I'm Stan Brown.
20 I am an engineer from the Center for Devices. I will
21 present the first half of the team effort between
22 myself and David Asher's group, which was funded by
23 the FDA Office of Science, and these data, some have
24 been published. Some are preliminary. Some are in
25 manuscripts in preparation, and this is not good news

1 on the screen.
2 Basically, what we were doing in my side
3 of town was to look at four questions. The first
4 question is can you safely autoclave in sodium
5 hydroxide without wrecking your autoclave? The second
6 question is what are the effects of the WHO protocols
7 on surgical instruments? The third part of that was
8 to develop an experimental instrument that could be
9 used in a simulated instruments contamination study
10 that would be compatible with the hamster model that
11 David Asher has. And the fourth was to do some --
12 there we go. Okay. Let's click through here.
13 First of all, instruments from CDRH, we
14 were thinking about primarily reuse, as you have
15 heard, or reusables, but there is also growing concern
16 about these things called SUDs or single-use devices,
17 and with the law we are now reevaluating how we assess
18 the reprocessing and validation of some of the
19 reusables, particularly those that are neurological or
20 other type of tissue contact. From the CBER point of
21 view, as you know, we are talking about contact of
22 instruments that you use for tissue preparation.
23 Next. Disclaimer. We developed these
24 methods, because they fit within the financial
25 constraints and the laboratory constraints. In our

1 laboratories, these presentations do not constitute a
2 regulatory endorsement for these methods. They are
3 simply methods we thought would get answers that we're
4 after.
5 Next. You know all about this story and
6 we're primarily interested in the sodium hydroxide
7 autoclaving phase and the soaking in sodium hydroxide
8 or bleach.
9 Next. So if you go to the CDC website,
10 you will see that there are a couple of warnings. One
11 is that if you autoclave in sodium hydroxide, you
12 wreck your autoclave and two, if you soak in bleach,
13 you will wreck your instruments. And these are based
14 on the studies that we started a few years ago, and I
15 think CDC may actually have now inserted the reference
16 from our work on that.
17 Next. Again, there are the four questions
18 that we are trying to answer.
19 Next. The first one has just been
20 published in the American Journal of Infection Control
21 with Kathy and myself.
22 Next. She did the work and I wrote the
23 paper, so I got to be first author. And again, the
24 question is the autoclave manufacturer said if you
25 autoclave in sodium hydroxide, you don't have a

1 warranty on your autoclave. Knowing, of course, this
2 must be done in a gravity displacement, so it doesn't
3 fit in the standard central storage big prevacuum type
4 autoclave. It has got to be controlled with a liquid
5 cycle.
6 Next. Two approaches. One was we would
7 put a liter of sodium hydroxide in a pan and cover it.
8 Two, we would put some sodium hydroxide in a beaker
9 and put the beaker in a pan and cover it. And then we
10 put it in an autoclave. We did repeat one hour
11 sterilizations, and we did these at 134C just to be a
12 little more extreme, and we did them for an hour, up
13 to five cycles, and we put pH paper inside, outside,
14 everywhere. We put pH meters inside and outside, and
15 it is a closed system for the little tabletop with six
16 liters of water reservoir. We put it through five
17 cycles to see what happens to the water in the
18 reservoir to see, again, what happens to the
19 autoclave.
20 Next. And we got thinking about pans and
21 lids. This one probably, the condensate will get on
22 the top and drip down and wreck your autoclave. This
23 one, it might wreck your autoclave and it might drip
24 inside. Some of them have little nipples or
25 construction bars. To me, that is a Black Iron Dutch

1 Oven where these drips, so that they roast while
2 you're doing it. And then you have got some that
3 actually have gutters that contain the lid within the
4 pan. So part of this is what kind of pan and lid
5 design you have.
6 Next. The two that we used successfully
7 was a Nalgene Instrument tray shown here. This was
8 filled with a liter of sodium hydroxide and closed.
9 Next slide. And if you look here, you can
10 see this is a drain on that gutter, so the condensate
11 goes back into the pan. It doesn't go out.
12 Next. And there you see the lid that is
13 fully contained within the gutter and, of course, this
14 has been used for years. It's for control of human
15 waste and biohazards.
16 Next. The other type of pan was a Lid
17 (D), which has a lip on the lid. It also has
18 crossbars that act as condensate drip spots.
19 Next. And the results of this were no pH
20 changes outside the containment. Inside the lids were
21 very caustic. The bottom of the pans were very
22 caustic. There was lots of vaporization, condensation
23 going inside, but it was all contained within the
24 containment vessel. So we conclude that if you use
25 this kind of -- if you use the right kind of pans and

1 lid, you can do it without wrecking your autoclave.
2 And, of course, those of you who have been doing this
3 in the lab for years know that. Obviously, hot
4 caustic is hot and you have to be careful. It
5 probably cannot be done in a standard central storage
6 autoclave and it may require larger approved type
7 pans.
8 Next question. What do these things do to
9 your instruments? Next. What we did was we bought
10 surgical instruments from Roboz, which is a medical
11 device supplier in Rockville, and we bought lab stuff
12 from VWR. Some of them are labeled Germany with CE
13 marks and some of them were labeled Pakistan, and
14 there are some members in the audience who will
15 appreciate this. We put them through repeat cycles of
16 the WHO including autoclave and water.
17 Next. And here you see some carbide
18 tipped needle holders. This one has been through five
19 times autoclave and sodium hydroxide, five hours in
20 sodium hydroxide. There is a little bit of blackening
21 in the box joint. This one was soaked for one hour in
22 Clorox, and you can see there is a tremendous amount
23 of corrosion going on at the box joint and around the
24 carbides.
25 Next. These had beautiful gold handles,

1 high quality instruments, and that is one hour in
2 bleach. So if you got gold handles, don't bleach
3 them. This is five times gold handles autoclaved in
4 sodium hydroxide. It looks fine.
5 Next. This is a German pair of scissors
6 versus a Pakistani pair of scissors, five times in
7 sodium hydroxide. You can't photograph shiny, but
8 this is shiny. It just looked great, and this looked
9 really dark and dingy.
10 Next. This is Germany versus Pakistan,
11 and you notice the Roboz label on this thing as
12 stainless steel, and this tubing clamp around this
13 weld really took it with the Clorox. This tubing
14 clamp after five hours in bleach, this is the 6
15 percent, which is what, 2,800 parts per million. It
16 looked fine. So some go, some are fine.
17 Next. So the conclusion of this, and I
18 didn't show you any pictures. Titanium really does
19 not like sodium hydroxide, and this is well-known in
20 the material science literature, as well. Soaking in
21 sodium hydroxide, they couldn't care less, none of
22 them. Soaking in bleach, some did fine, some didn't.
23 The problems were the gold handles and the welds. But
24 the important message here is if it's going to
25 corrode, it's going to do it first time. So you don't

1 have to do a long experiment. If you put it in Clorox
2 and it comes out rusty, you know it's going to rust
3 and you go on and find a better instrument.
4 Next. So Part 3. We wanted pins and this
5 is part to lead into an animal model of the simulated
6 instrument for David's studies. He was using a 25
7 gauge needle on a half cc syringe in his animal work
8 for injection, and we wanted to make pins instruments
9 that were like that, but we also wanted to be able to
10 suspend them over 96 weld plates, so we could do
11 serial dilutions of bacteria, viruses in brain
12 homogenate, and the system needed to be autoclavable.
13 Next. So there is the syringe needle that
14 he was using. That is a good old copper penny, and
15 what we did was we took Eppendorf tips. My wife is a
16 microbiologist, and so is Kathy. We took half
17 millimeter stainless steel pins. We took some epoxy.
18 We used the Eppendorf to draw the epoxy up into the
19 tip, stuck the metal pin into it, hung it in a rack,
20 put it in an oven to cure and now, you have things
21 that can be autoclaved, and it's the same size as the
22 needle that is used. So from an ergonomics point of
23 view, it's something that he would feel comfortable
24 with, I think.
25 Next. And here, you see the setup. This

1 is your standard Eppendorf rack with modified
2 stainless screws to adjust the height, and the pins
3 were sitting in the wells of a 96 weld plate, and
4 Kitty, that after a little bit of practice, she could
5 actually get all the needles into all the holes,
6 right?
7 Next. Finally, we wanted to do some
8 preliminary of adhesion of both blood and tissue and
9 looking at WHO protocols, and one question was what
10 about damage and adherence? So we were using
11 stainless steel pins and we also made pins out of
12 piano wire, which really did not have a good time in
13 Clorox.
14 Next. Pins are placed in a rack and stuck
15 into a slab of liver for an hour, and then we left to
16 dry as a worst case. The pins were stuck in a 96 weld
17 plate in sheep's blood for an hour, and then they were
18 left to dry. We went through ultrasonic cleaning,
19 which the standard protocol is 60 degrees C with an
20 enzyme cleaner. We autoclaved in sodium hydroxide.
21 We soaked in bleach and we got unclean controls.
22 The results were the unclean ones, that
23 the protein was more adherent from liver than it was
24 from blood, and the amount was using Bradfords
25 reagent. It's about the equivalent of -- our minimum

1 was one microliter detection limit. Damaged pins did
2 not seem to be more adherent, so that the blackening
3 in the box from autoclaving and sodium hydroxide is
4 probably not a problem. Repeat exposure did not show
5 accumulative effect.
6 Next. So then Kathy wanted to do some
7 bacteriology, and she soaked them in a solution of
8 staph epi. for 24 hours, let them dry and did the same
9 kind of cleaning things, and then stuck them into an
10 agar in a test tube and incubated for 24 hours.
11 Next. Lo and behold, autoclaving in
12 bleach killed everything. So we had to try some
13 modified WHO. So we dropped the sodium hydroxide
14 autoclave and the ultrasonic cleaning was done at room
15 temperature.
16 Next. So what we found was that only the
17 pins and bleach showed no growth, but, of course, we
18 don't know if we cleaned it or we just killed them.
19 The other produce showed fewer protocol than the
20 untreated control, but bacteria was still present.
21 And then the question is are we cleaning or are we
22 just killing?
23 Next. And we tried some SEM work, and you
24 can see a little small column of staph epi. here on
25 the uncleaned tip. It was very unconvincing in terms

1 of whether we really were cleaning or we were just
2 killing.
3 Next. So our conclusions were, first of
4 all, yes, you can safely autoclave in sodium hydroxide
5 with the right pan and lid. Some WHO protocols can
6 damage some instruments. Discoloration does not seem
7 to impair function or cleaning. The bacteria leave a
8 lot of unanswered questions, and the questions for
9 prions, of course, we don't touch them in CDRH, that
10 is David's role.
11 So next, and I will turn the podium over
12 to David to talk about his hamster studies.
13 DR. ASHER: Thanks. You can go right to
14 the next slide, please. Thank you. I can't believe
15 that it's almost 6:00 and we're still giving talks.
16 Quite a few people in CBER participated in TSE related
17 activities. These studies are really involved only
18 people in CBER in my own little group, and especially
19 Kitty Pomeroy who I think is still here in the back.
20 Without her holding the whole enterprise together,
21 there is no way that we could have done this.
22 Next slide, please. And among the staff
23 at CDRH, of course, Kathy Merritt and Stan Brown, who
24 has just spoken, and I don't believe that we would
25 have gotten the funding to do what we have been able

1 to do without Stan's efforts.
2 Next slide, please. We have developed two
3 simple methods to evaluate methods for decontamination
4 of TSE agents dried on surfaces. In this talk, I am
5 going to concentrate on two regimens that more or less
6 replicate recommendations of the World Health
7 Organization consultation. We used two general models
8 for both of which 263K scrapie was the agent.
9 The first model was a modification of a
10 method for evaluating virucides that was described
11 years ago by John Chen of the Environmental Protection
12 Agency. He dried viral agents onto glass cover slips,
13 treated them and then assayed residual virus.
14 The second method was stimulated by two
15 reports from Charles Weissmann's group, and Professor
16 Weissmann will speak here tomorrow morning. They
17 dried scrapie agent onto steel wires implanted into
18 mouse brains. We didn't do that, but as you saw from
19 the devices that Stan showed you, our model was very
20 similar.
21 Years ago, we had done a couple of
22 experiments with model squirting scrapie through
23 actual hypodermic needles, but it was very cumbersome,
24 and we never followed up on it. We have used the
25 first method.

1 Next slide, please. The first method for
2 many years, simply dropping suspensions of scrapie
3 infected hamster brains onto glass cover slips.
4 Next slide, please. Then they are dried
5 in a petri dish in a hood.
6 Next slide. And then they can be exposed
7 to any number of disinfectant or decontamination
8 regimens, here potassium permanganate solution that
9 can be autoclaved, that can be soaked. You can do all
10 kinds of things with it.
11 Next slide, please. Then they can be
12 ground up and supernatant fluid assayed. Now, we used
13 plastic pipettes and tubes for the whole procedure,
14 because they are disposable. We don't have to worry
15 about potential carryover of infectivity. Although,
16 the original method described by Chen used 10 brack
17 tissue grinders of the kind seen here. So the slips
18 are ground up in an ml of diluent.
19 Next slide, please. The glass is allowed
20 to settle out, and then the supernatant fluids are
21 assayed for infectivity by intracerebral injection of
22 hamsters.
23 Next slide. If the hamsters get sick,
24 their brains are removed and then they are checked for
25 protease resistant prion protein as evidence that

1 scrapie agent was present and was not eliminated by
2 the decontamination regimen.
3 Next slide, please. For reasons that may
4 become clear at the end of this talk, I have about six
5 minutes left, we think that it might be useful to do
6 immunohistochemistry on some of these brains, as well.
7 Although, we haven't done that yet.
8 Next slide, please. One advantage of the
9 method is that you can rid of residual toxic
10 disinfectants, Robert Somerville talked about that
11 problem this morning, by simply rinsing the cover
12 slips in distilled water to get rid of things like
13 Clorox, which is really terrible for assay animals.
14 As you see here, this is sort of an upside
15 down dose response curve. It's hamster survival times
16 plotted against the dilution of supernatant fluid.
17 And here are three curves, one for unsoaked or dipped
18 slides, one that has been soaked in water, and the
19 other that was soaked in water and then dipped in
20 water a second time. And you can see that they are
21 virtually superimposable. None of the infectivity
22 appeared to come off on this exposure to distilled
23 water.
24 Next slide, please. And it was using this
25 method that we first demonstrated the resistant

1 fraction of infectivity that survived drying on glass
2 and then prolonged exposures to steam autoclaving at
3 elevated temperatures.
4 Next slide. To investigate some of the
5 performance characteristics of the model, you can
6 imagine doing many, many assays in hamsters is
7 extremely cumbersome. We tried drying specimen
8 samples of polio virus and two other viruses suspended
9 in brain onto glass, and then titrating multiple
10 samples. The results summarized here suggest that the
11 agreement from test to test and day to day was
12 reasonably good, but that there was enough
13 variability, so that a controlled titration really
14 should be done in each test. And it might even be
15 reasonable to consider putting in a test
16 decontamination, a reference decontamination
17 treatment. Although, we have never had enough
18 resources to support that.
19 Next slide, please. When we began to work
20 with the scrapie brain suspensions dried onto the
21 steel needles that Stan Brown has just showed you, we
22 decided first to do some similar preliminary studies
23 with conventional virus suspended in saline containing
24 10 percent brain extracts to get some idea of how the
25 scrapie agent might be expected to behave, so we

1 wouldn't waste months and months on a model that
2 wouldn't get enough infectivity on.
3 But we were surprised when neither polio
4 virus nor porcine parvo virus suspended in brain
5 appeared to stick to the steel needles at all or at
6 least we couldn't detect any of them in cell culture
7 assays. We had no trouble getting them to stick to
8 glass, but we couldn't find detectable porcine parvo
9 virus or polio virus dried onto steel needles.
10 So now wanting to take a chance that we
11 would set up our test with the limited funding
12 available and the find that we hadn't had enough
13 challenge agent stuck to the steel needle, so we
14 decided to suspend the 263K scrapie hamster brain in
15 a normal brain paste, and we used a calf brain as the
16 source of the normal brain material.
17 Next slide, please. I must say we decided
18 to check out our concern. We had enough hamsters to
19 do a rough titre of 263K scrapie diluted in phosphate-
20 buffered saline without any additional brain material,
21 and it appears that the scrapie infectivity in the
22 saline suspension did stick to the steel wires. You
23 will notice we get positives out to a dilution of 10-
24 5, so that the behavior of the polio virus and the
25 porcine parvo virus does not appear to have predicted

1 the behavior of the scrapie agent.
2 But the studies that I am going to
3 summarize in the next few slides use scrapie infected
4 brains as a paste to charge the needles. The glass
5 was charged in the way that I described previously
6 with saline suspensions.
7 Next slide, please. So let me summarize
8 for you the general design of the efforts. We looked
9 at two variations of two kinds of decontamination
10 regimens that generally resemble those recommended by
11 the WHO consultation, and then after that, I will add
12 some other results that we thought you might find of
13 some interest.
14 First, as we have mentioned, infected
15 brain is dried on the objects, either a saline
16 suspension on glass slides or tissue paste onto steel
17 needles. Then come the decontamination steps, which
18 are either a chemical soak in one normal sodium
19 hydroxide in the autoclave for 30 minutes or a soak in
20 sodium hypochlorite, full strength chlorine bleach
21 from the grocery store at room temperature for 60
22 minutes followed by an autoclaving at 121 celsius for
23 30 minutes or at 134 celsius for 90 minutes. The
24 autoclaving with sodium hydroxide is in the sodium
25 hydroxide. The autoclaving with bleach is after it is

1 in water.

2 Following that, all these materials were
3 cleaned in an ultrasonic cleanser using a laboratory
4 proprietary detergent with a pH of 9.45. All of them
5 got this, because, as pointed out by Dr. Rutala, it is
6 important to try and replicate the conditions under
7 which these things would be done in a hospital. The
8 sonic cleaner was cranked up the highest temperature
9 that it would take, which was over 60 degrees,
10 although, somewhat variable, and for the longest time
11 the timer kept, which was for 90 minutes.

12 This was done by putting each object into
13 a separate tube filled with the cleaner, and then the
14 tubes were immersed in more cleaner in the chamber.
15 Following that, there was a water rinse and then,
16 finally, a terminal sterilization in the autoclave at
17 121 celsius for 20 minutes in order to model what we
18 took to be standard hospital practice.

19 Next slide, please. As I mentioned, the
20 sonicator was set at maximum temperature and time. We
21 only did the one set of conditions. We made no effort
22 to select a better cleaning solution. I am sure there
23 are many others, that many others are available.

24 Okay. Next slide, please. First, the
25 assay technique for residual infectivity on the glass

1 slips. Each experiment, a positive control consisting
2 of 10 slips each holding .1 ml of dried on scrapie
3 infected, 10 percent hamster brain dried down, not
4 exposed to any decontamination regimen, ground to a
5 powder and a ml of PBS glass allowed to settle.
6 Fluids were then pooled, tenfold dilutions performed
7 in phosphate-buffered saline, each dilution assayed in
8 four hamsters, the same volumes that Dr. Rau showed
9 you, .03 ml each intracerebrally into the left frontal
10 lobe. That is simply so that we would know in each
11 test how much infectivity had been used.
12 Next. Hang on a second. Let me finish.
13 Each of 10 slips then was exposed to some
14 decontamination regimen, and then also ground to a
15 powder in phosphate-buffered saline, the fluid assayed
16 as for the controls, so that each experiment on glass
17 involved 10 slips and 40 hamsters.
18 As David Taylor had mentioned to you
19 earlier, we deducted incidental deaths. We took 45
20 days as the cutoff between considering it a death
21 incidental. Perhaps we shouldn't have done that.
22 Next slide, please. For the steel
23 needles, the positive controls were tenfold, dilutions
24 of infected hamster brain as a 10 percent paste in
25 normal calf brain, and then serial dilutions were done

1 with normal calf brain paste. Four needles were
2 charged for each dilution, dried and then a separate
3 hamster was assayed for each needle. For the actual
4 test, 40 needles charged with 10 percent hamster brain
5 and normal calf brain, dried, tested and then assayed
6 as for the control above. Less incidental deaths
7 occurring before four days.
8 Next slide, please. This is just to show
9 you what a titration on glass looked like, the interim
10 score here at eight and a half months. Notice that
11 the last positive animal so far as those inoculated
12 with a dilution of 10-8 calculated from the original
13 brain tissue.
14 Next slide, please. And a similar
15 titration for scrapie dried onto steel needles, also
16 positive to a reasonably high dilution. Actually,
17 somewhat higher than we got with the saline
18 suspension, so we weren't sorry that we had used the
19 brain paste.
20 And you might notice that there is one
21 negative at the lowest dilution. That was an animal
22 that died at 55 days. Brain was negative, and that is
23 why we're wondering whether 45 days might have been
24 the best date to estimate incidental deaths.
25 Next slide, please. Before I move on to

1 the actual results, we were interested to see what
2 ultrasonic cleaning in hot alkaline detergent alone
3 without any other treatment would do, so we did a
4 titration from that and found a substantial reduction,
5 both of the infectivity on glass and on steel needles
6 from the hot ultrasonic cleaning alone. The log
7 reduction factor is slightly over 5 logs. Although,
8 for both models there was some residual infectivity
9 left on the surface.
10 Again, we made no effort to optimize, to
11 modify or optimize the procedure. We presume that
12 most of the infectivity probably went into the liquid,
13 but we haven't made any attempt to find out whether
14 that is true.
15 Next slide, please. So here are the WHO
16 studies. After exposure of glass slips, there are the
17 glass slips, to sodium hydroxide or to sodium
18 hypochlorite with autoclaving at either 121 celsius or
19 at 134 celsius, there was obviously a dramatic removal
20 of infectivity, but darn, one of the animals assaying
21 material exposed to one normal sodium hydroxide at 134
22 autoclave, 134 celsius for 90 minutes has come down
23 positive.
24 Next slide, please. And similar
25 experiments with steel yielded relatively similar

1 results, at least two, maybe three of the assay
2 animals have had positive Western Blots. We are going
3 to have to check those out. Obviously, these stray
4 positives have been seen before, and we have to
5 convince ourselves as to whether they are really
6 positives or whether it's inadequately digested PrP in
7 the Western Blot or whether it's real.
8 So the methods are, obviously, highly
9 effective. They saved almost all the hamsters and
10 removed so much infectivity that most of the objects
11 assayed didn't show evidence of contamination.
12 Remember that each of these objects was charged with
13 at least a million lethal doses of scrapie agent, but
14 we can't say that they are perfect.
15 Next slide, please. We have seen similar
16 results in the past using single chemical soaks.
17 These are all done with the Chen glass test. And,
18 again, we have frequently seen, these are sodium
19 hydroxide soaks at various temperatures, an occasional
20 stray positive.
21 Next slide. Some tests have found no
22 positives at all, but remember with the Chen glass
23 test, we sample only about 12 percent of the
24 supernatant fluid from each slip, so that these
25 results are not necessarily different from the ones

1 that show single positives. There is a substantial
2 sampling problem when you're dealing with very small
3 amounts of infectivity.
4 Next slide, please. Here is another
5 result with sodium hypochlorite where we had no
6 positive animals. I marked these all as interim,
7 because we haven't finished all the Western Blots even
8 though some of these are not new experiments.
9 Next slide, please. And finally, I would
10 like to say that some other chemical agents are
11 probably also very effective. Here are some results
12 using concentrated formic acid, which is used to treat
13 tissues for histology and immunohistochemistry. Note
14 that there is only a single positive animal out of 37
15 tested. Reports of a commercial phenolic
16 disinfection, at least temporarily unavailable here in
17 the United States is reported to be very effective,
18 and we have heard that there are other decontamination
19 regimens in development not yet ready to share with
20 the FDA or the public that are showing promise.
21 Let me conclude now by, next slide,
22 please, just summarizing that methods developed to
23 evaluate the effects of virucides are adaptable to
24 evaluate decontamination of TSE agents. Studies with
25 two models both suggested that exposure to 263K

1 scrapie agent dried on surfaces to solutions of sodium
2 hydroxide, sodium hypochlorite with simultaneous or
3 sequential autoclaving and ultrasonic cleaning in hot
4 alkaline detergent markedly reduced amounts of
5 infectivity, and the risk that any object would retain
6 detectable amounts of agent.
7 Other chemical treatments may also be
8 effective, but uncertainties remain. One, the
9 reliability of the decontamination procedures, not
10 only the fact that we see stray positives, but also
11 there is a theoretical concern that the predictive
12 value of these results, the results from such models,
13 may not adequately predict the behavior of
14 decontamination regimens in the actual health care or
15 manufacturing setting, concern that there may be
16 sanctuaries of the kind that Bob Rohwer and David
17 Taylor have discussed that might occur in
18 manufacturing processes or health care setting that
19 would impair the ability of otherwise effective
20 decontamination regimens to act.
21 It is quite late, but I am happy to answer
22 questions for anybody who has got the energy still to
23 ask them. Thank you.
24 CHAIR PRIOLA: Are there any questions for
25 Dr. Asher or Dr. Brown? All right. If not, I --

1 okay, Dr. Somerville has one for you.
2 DR. SOMERVILLE: I'm just going to make a
3 brief comment about the first part of the talk, and
4 that is that in our experience, in our survey, we find
5 that the various different grades of stainless steel
6 are used from the manufacturer of surgical instruments
7 and with various different finishings, and they have
8 different responses to the kinds of treatment that
9 Stan Brown was trying on the instruments.
10 The one brief question I have is have you
11 tried anything other than visual inspection to see
12 what the degree of damage is being done to the
13 instruments?
14 CHAIR PRIOLA: Can Dr. -- oh, he is coming
15 up there. Dr. Brown can answer that.
16 DR. BROWN: The answer, at this point, is
17 we have done nothing other than visual, and part of
18 the next generation of study is to be looking at some
19 of the different alloys, some of the different
20 corrosion test methods. Some of these effects are so
21 blatant that why both to -- I mean, I cut up the gold
22 handles and put them in the SEM just to make sure it
23 really was gold.
24 And, in fact, there was gold on those
25 handles, but no, we haven't gone any further. But one

1 of the questions is are the different grades, you know
2 -- in talking with the instrument manufacturers and
3 the people who do chemical analysis of instruments,
4 there are a whole wide range of grades of stainless
5 steels, but the manufacturers will tell you what
6 probably is the most important is actually the
7 mechanical treatment in terms of how they make them,
8 coworking, etcetera. And it may not be a matter of
9 chemistry, but it's a matter of mechanical parts.
10 The finger rings very typically are
11 attacked by Clorox, and that is an area where there
12 has been a lot of mechanical cowork to form the rings.
13 Whereas, elsewhere on the same instrument, the surface
14 looks fine. So it's not just the chemistry, but it's
15 actually the mechanical processes used in the forming
16 or fabricating. And again, if it's going to go, it's
17 going to go the first time you throw it in bleach.
18 BOARD MEMBER HOGAN: Dr. Brown, before you
19 leave, I have one more question. Dr. Brown, could you
20 get rid of the black deposit that formed on the sodium
21 hydroxide instruments?
22 DR. BROWN: First of all, we didn't do any
23 other cleaning. We just over and over and over,
24 autoclave and bleach. We didn't use what do they call
25 it, milk, the cleaning milk that is used in standard

1 central storage.
2 BOARD MEMBER HOGAN: So you didn't try?
3 Is that it?
4 DR. BROWN: So what I did actually on some
5 of them is I did a bit of gentle scrubbing in the box
6 joints to see if it would come off. It wouldn't come
7 off much by general scrubbing. Actually, if you reuse
8 them, you can begin to wear off the blackening. But
9 it's really a very superficial kind of blackening, and
10 then the thing with the protein adherence with the
11 piano wire, they really did corrode and at least the
12 serum protein stuff we did didn't show any difference.
13 CHAIR PRIOLA: Dr. Edmiston?
14 DR. EDMISTON: I know it's late and I
15 don't want to hold anybody up, but I really want to
16 commend Dr. Asher and Dr. Brown. You are heading in
17 the right direction. The question that I have is do
18 you contemplate looking at this in devices that have
19 larger bores in terms of if you're looking at a hollow
20 device, are you looking at other devices that may have
21 a larger bore where the cleaning process may be
22 expedited, normal cleaning process may be expedited on
23 the basis of having a larger internal diameter?
24 DR. BROWN: These are solid pins.
25 DR. EDMISTON: These are solid pins?

1 DR. BROWN: These are solid pins. They
2 were not needles.
3 DR. EDMISTON: Okay.
4 DR. BROWN: So the idea was that David had
5 been using a needle. He was used to the feel of that
6 size needle, and I made solid pins to match. So these
7 were not hollow.
8 DR. EDMISTON: So you don't know what
9 would happen with a hollow bore device?
10 DR. BROWN: No. One can sort of guess,
11 but I think --
12 DR. EDMISTON: Right.
13 DR. BROWN: You know, this term of, you
14 know, the nooks and crannies and the hiding places, I
15 think that's the next generation of the studies.
16 Polymer coated, we have got some that, apparently, are
17 even teflon coated that are part of the next step in
18 the study.
19 DR. ASHER: Yes. As I mentioned, years
20 ago I did some standard hypodermic needles, just
21 squirting suspensions of scrapie through and letting
22 the needles dry and autoclave. You know, you're not
23 surprised to hear that they were not sterilized.
24 DR. EDMISTON: I think our experiences
25 have been that, especially in the case of

1 neurosurgery, that those patients who fall into that
2 risk category, a lot of us are moving towards the use
3 of disposable biopsy needles.
4 CHAIR PRIOLA: Dick, did you have a
5 question? I'm sorry, can you what?
6 BOARD MEMBER JOHNSON: Can we leave our
7 papers behind?
8 CHAIR PRIOLA: I think you --
9 SECRETARY FREAS: If you want it tomorrow
10 morning, I would really recommend you take it to your
11 room. I do have a couple of quick announcements.
12 This morning, we passed out about 200 Conflict of
13 Interest questionnaires and we got about five of them
14 back. I would like to encourage you to look at the
15 questionnaires and if you could drop them off on your
16 way out, we'll pass out another 100 tomorrow and,
17 hopefully, we'll got some back.
18 Also, somebody left behind a Palm Pilot.
19 It looks like it's a very expensive Palm Pilot, and if
20 you can identify it, it's yours. Tomorrow morning,
21 we'll be seeing you at 8:00 sharp.
22 CHAIR PRIOLA: Okay. I would like to
23 thank all of the speakers for presenting published and
24 unpublished data to the Committee, and we're adjourned
25 until 8:00 a.m. Thank you.

1 (Whereupon, at 6:18 p.m. the meeting was
2 adjourned.)
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