

UNITED STATES OF AMERICA
DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

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TRANSMISSIBLE SPONGIFORM ENCEPHALOPATHIES

ADVISORY COMMITTEE

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MEETING

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WEDNESDAY, APRIL 23, 1997

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The meeting was held in Versailles Rooms I and II, Holiday Inn Bethesda, 8120 Wisconsin Avenue, Bethesda, Maryland 20879, at 9:00 a.m., Paul W. Brown, M.D., Chairman, presiding

PRESENT:

PAUL W. BROWN, M.D., Chairman
WILLIAM FREAS, Ph.D., Executive Secretary
LINDA A. DETWILER, DVM, Member
LEON FAITEK, Member
BARBARA W. HARRELL, MPA, Member
DAVID G. HOEL, Ph.D., Member
KAREN HSIAO, M.D., Ph.D., Member
KATHERINE O'ROURKE, Ph.D., Member
RAYMOND P. ROOS, M.D., Member
LAWRENCE B. SCHONBERGER, M.D., Member
EDMUND C. TRAMONT, M.D., Member
GILBERT C. WHITE II, M.D., Member
SIDNEY M. WOLFE, M.D., Member

PRESENT: (continued)

ERIC A. DECKER, Ph.D., Temporary Voting Member
HANS P. RIEMANN, DVM, Ph.D., Temporary Voting
Member
J. MICHAEL DUNN, Ph.D., Industry Liaison
DONALD P. WRATHALL, Ph.D., Industry Liaison
JOHN GRAY, DVM, Guest Speaker
ROBERT ROHWER, Ph.D., Guest Speaker
REINHARD SCHRIEBER, Guest Speaker
GERALD M. WISEMAN, Guest Expert
THOMAS HIGGINS, Public Comment

FDA PRESENTERS:

PHILIP M. BOLGER, Ph.D.
KIKI HELLMAN, Ph.D.
JOHN HONSTEAD, DVM
MIKE DiNOVI, Ph.D.
JOHN VANDERVEEN, Ph.D.
CAROL VINCENT, M.S.
RANDY WYKOFF, M.D.

ALSO PRESENT:

DAVID ASHER, M.D.
PAULA BOTSTEIN, M.D.
JOHN B. BAILEY, Ph.D.
FLORENCE FANG, M.S.
PAUL RICHMAN, Ph.D.
EDWARD TABOR, M.D.

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Time: 8:57 a.m.

DR. FREAS: Good morning. If you would take your seats, please, we'd like to go ahead and get this meeting started.

Good morning. I am Bill Freas, and I am the Executive Secretary for the Transmissible Spongiform Encephalopathies Advisory Committee, and I would like to welcome you here this morning.

Before I begin, though, I would like to thank the new members who are seated around the table for adjusting their schedules at the last minute to come and make today's meeting. They've gone through a lot, and they deserve my thanks and the thanks of my colleagues at FDA for their efforts, just getting here, and we're very appreciative and would like to thank you.

I am the designated Federal official for this meeting. If anybody in the audience would like to communicate with the members on the Committee, please do not directly approach either the Chair or any Committee member. Please see me, and I will relay your requests to the Chair and the Advisory Committee for consideration.

So please leave our Committee members,

1 especially during breaks -- Let them take their break.
2 Come and see me. I'll be right up here in the front
3 of the room, and I will relay any information or
4 request that you have for the Committee to the
5 Committee members.

6 Both today and tomorrow's session will be
7 open to the public. So you're welcome to stay for the
8 full meeting, both today and tomorrow, as outlined in
9 this morning's agenda.

10 I would like at this time to go around the
11 head table and introduce to the public the members who
12 are seated at the head table.

13 Starting on the audience's righthand side
14 of the room, the far side of the table, is Mr. Leon
15 Faitek, a consumer advocate on this committee. If you
16 would raise your hand, just so those sitting in the
17 back of the room can identify you.

18 Sitting next to Mr. Faitek is Dr. William
19 Hueston, Associate Dean, Virginia-Maryland Regional
20 College of Veterinary Medicine. A lot of these are
21 new members, and my memory is not real good. So I
22 appreciate -- I'm not asking you to raise the hands
23 for the public. I'm asking you to raise your hand so
24 I can see you.

25 The vacant seat there will be filled by

1 Linda Detwiler. She will be arriving very shortly.
2 She notified us she's running a little late. She's
3 Senior Staff Veterinarian, U.S. Department of
4 Agriculture.

5 The next individual is Dr. David Hoel,
6 Professor and Chairman, Department of Biometry and
7 Epidemiology, Medical University of South Carolina.

8 Next is Ms. Barbara Harrell, our consumer
9 representative, Director of Minority Health, State of
10 Alabama Department of Public Health.

11 Next is Dr. Lawrence Schonberger,
12 Assistant Director for Public Health, Division of
13 Viral and Rickettsial Diseases, Centers for Disease
14 Control.

15 Next is Dr. Sidney Wolfe, Director, Public
16 Citizen Health Research Group, Washington, D.C.

17 Around the corner is Dr. Gilbert White,
18 Professor, Department of Medicine, University of North
19 Carolina.

20 Next is Dr. Karen Hsiao, Associate
21 Professor, Department of Neurology, University of
22 Minnesota.

23 Next is Dr. Raymond Roos, Chairman,
24 Department of Neurology, University of Chicago.

25 Next is the Chairman of this Advisory

1 Committee, Dr. Paul Brown, Medical Director, National
2 Institute of Neurological Disorders and Stroke, NIH.

3 The vacant seat will be filled by myself.

4 Next is Dr. Katherine O'Rourke, Research
5 Microbiologist, U.S. Department of Agriculture,
6 Washington State University.

7 Next is Dr. Edmund Tramont, Professor of
8 Medicine, Medical Biotech Center, University of
9 Maryland.

10 Next is Dr. Hans Riemann, a temporary
11 voting member for today, Department of Preventive
12 Medicine, College of Veterinary Medicine, University
13 of California Davis.

14 Next is Dr. Eric Decker, a temporary
15 voting member for today, Associate Professor,
16 Department of Food Science, University of
17 Massachusetts.

18 Next is Dr. Elizabeth Williams, another
19 temporary voting member for today, Professor,
20 Department of Veterinary Science, University of
21 Wyoming.

22 Next are two industry representatives.
23 They are Dr. Michael Dunn, Manager, Pharmaceutical and
24 Edible Technical Services, Kind & Knox Gelatine, Inc.,
25 Sioux City, Iowa.

1 Next is Dr. Donald Wrathall, Senior
2 Technical Associate, Eastman Gelatine, Peabody,
3 Massachusetts.

4 Hopefully, that is everybody. There are
5 two members that were, because of --

6 Dr. Wiseman is a guest that has been
7 invited to the table this morning. Dr. Wiseman, thank
8 you for joining us at the table. Dr. Wiseman is not
9 a member of the Committee, but he has been invited to
10 the table so that he will be close to a microphone to
11 contribute to this morning's discussion.

12 There are two members of the Committee who
13 could not make it today. They are Dr. Lawrence
14 Lessin, Medical Director, Washington Cancer Institute,
15 and Dr. Stanley Prusiner, Professor of Neurology,
16 University of California School of Medicine.

17 I would now like to read into the public
18 record the conflict of interest statement for this
19 meeting.

20 This announcement is made part of the
21 public record to preclude even the appearance of a
22 conflict of interest at this meeting of the
23 Transmissible Spongiform Encephalopathies Advisory
24 Committee on April 23rd and 24th, 1997.

25 Pursuant to the authority granted under

1 the Committee charter, the Director of the Center of
2 Biologics Evaluation and Research has appointed Dr.
3 Elizabeth Williams as a temporary voting member. The
4 Director of the Center of Food Safety and Applied
5 Nutrition has applied Doctors Hans Riemann, Eric
6 Decker, as temporary voting members.

7 General waivers of applicability have been
8 approved for all participants. At this meeting only
9 general matters will be addressed by the Committee.
10 Therefore, it has been determined that all interests
11 that have been reported by the participants present no
12 potential for a conflict of interest at this meeting
13 when evaluated against the issues on the agenda.

14 Copies of all waiver statements addressed
15 in this announcement are available by written request
16 under the Freedom of Information Act.

17 With respect to FDA's invited guests and
18 speakers, the agency has determined that the services
19 of these guests and speakers are essential. The
20 following reported interests are being made public to
21 allow meeting participants to objectively evaluate any
22 presentation and/or comments made by guests and
23 speakers.

24 The interests are as follows: Dr. J.
25 Michael Dunn has disclosed that he is employed by Kind

1 & Knox Gelatine, Inc. Dr. John Grey, an employee of
2 the United States Department of Agriculture, USDA, as
3 part of his official duties is involved in the
4 regulation of animal products such as gelatin.

5 Dr. Robert Rohwer has conducted an
6 assessment of the risk of BSE contamination of bovine
7 derived gelatin for a Washington, D.C. law firm which
8 represents the gelantine industry before FDA. Dr.
9 Rohwer has received a fee for these services.

10 Dr. Reinhard Schrieber is employed by the
11 Deutsche Gelatine-Fabriken Stoess in Germany.

12 Dr. Gerald Wiseman has stocks for
13 retirement income from Philip Morris, his parent
14 company, and former holder at Kraft Foods-Atlantic
15 Gelatine.

16 Dr. Donald Wrathall is employed as Eastman
17 Gelatine -- is employed by the Eastman Gelatine
18 Corporation.

19 With respect to all other participants at
20 this meeting, we request in the interest of fairness
21 that they address any current or previous financial
22 involvement with any firm or product that they may
23 wish to comment upon.

24 So ends the reading of the conflict of
25 interest statement for this meeting.

1 Dr. Brown, I turn the meeting over to you.

2 CHAIRMAN BROWN: Good morning. My name is
3 Dr. Paul Brown. I have been designated the Chairman
4 of the Committee, the Advisory Committee for
5 Transmissible Spongiform Encephalopathy problems,
6 advising the FDA.

7 The meeting has been called to reconsider
8 the safety of imported and domestic gelatin
9 byproducts, gelatin and gelatin byproducts,
10 particularly with respect to any risk that might be
11 posed by the spongiform encephalopathy of cattle,
12 bovine spongiform encephalopathy.

13 The format of today's meeting will be
14 principally the allowing of public comments and
15 statements relative to these issues, followed by a
16 number of educational lectures given to us by invited
17 speakers with expertise in this field, and the
18 Committee at the table based on what they hear today
19 and tomorrow morning will try to achieve a consensus
20 with respect to advice given to the FDA concerning
21 this topic.

22 To welcome and provide you with further
23 introduction, I'm happy to introduce Dr. Randy Wykoff,
24 who is the Associate Deputy Commissioner for
25 Operations of the Food and Drug Administration. Dr.

1 Wykoff.

2 DR. WYKOFF: Thank you, Dr. Brown,

3 I am Randy Wykoff, the Associate
4 Commissioner for Operations at the FDA, and it is my
5 pleasure this morning to represent Dr. Michael
6 Friedman, who is the lead Deputy Commissioner at FDA.
7 On Dr. Friedman's behalf and on behalf of all of my
8 colleagues at FDA, I'd like to welcome all of you to
9 this meeting of the Transmissible Spongiform
10 Encephalopathy Advisory Committee.

11 This is an important meeting, and we
12 sincerely appreciate all of your willingness to be
13 here. The Advisory Committee process is a vitally
14 important process for the FDA. As some of you may
15 know, we have over 40 advisory committees at FDA that
16 advise us on the full range of issues for which we
17 have regulatory responsibility.

18 I believe, as do many of my colleagues,
19 that the advisory committee process is one of the most
20 valuable resources available to the FDA. Let me
21 outline for you four particular areas where I think
22 the advisory committee can be valuable to us at FDA.

23 First of all and most obviously, the
24 advisory committee allows us to have access to the
25 world's leading experts on issues of public health

1 importance. While we are very proud at FDA of the
2 quality of our scientists, and while we have very good
3 working relations with our sister Federal agencies,
4 the ability to bring in the world's experts on short
5 notice to advise us on issues of public health
6 importance makes the advisory committee literally
7 irreplaceable.

8 This advisory committee today will be
9 asked to review issues related to transmissible
10 spongiform encephalopathies and whether they pose any
11 risk to the safety of gelatin and gelatin byproducts
12 in this country.

13 Again, the ability to turn to experts of
14 this caliber on such short notice to address issues of
15 this importance makes advisory committees extremely
16 important, but that is not the only area where the
17 advisory committee can be important.

18 A second area where the advisory committee
19 process is of vital importance to us at FDA is the
20 fact that the advisory committee process allows us to
21 have public input into our deliberations. Because of
22 the laws under which we operate at FDA, it is
23 frequently very difficult for us to have input from
24 the general public.

25 We hope that, during the open public

1 comment section and subsequently by written
2 submissions, that the members of the public will feel
3 free to comment to FDA not only about this specific
4 issue, but about any other issues of relevance to TSEs
5 that are concern to the public.

6 A third area where the advisory committee
7 process can be very important to us at FDA is that we
8 have learned over the years that the advisory
9 committee process can sometimes be a most effective
10 mechanism that we have for educating the public about
11 issues of complex public health importance.

12 We hope that this meeting, with the help
13 of our colleagues from the media, will serve to
14 educate the general public about issues related to the
15 spongiform encephalopathies without causing undue or
16 unwarranted concerns.

17 The final -- The fourth and final area
18 where advisory committees can be of particular value
19 to the FDA is that advisory committees can serve as a
20 check on the actions and activities of the agency, a
21 mechanism by which outside experts can independently
22 tell us whether the actions that we are taking are the
23 most balanced, the most rational, and the most
24 appropriate actions to protect the public health.

25 We particularly look to the committee

1 today to advise us on whether the exemption of gelatin
2 from our recently proposed ruminant feed draft rule is
3 the most balanced and most rational way to protect the
4 public health.

5 To serve all of these ends, the committee
6 will be asked specific questions this morning, and Dr.
7 Hellman will outline these questions later after our
8 presentation. Obviously, we look forward to the
9 committee's answering these questions, but as I said
10 earlier, if the committee wishes to give us other
11 advice after they've answered those questions, they
12 are free to do so.

13 In answering the questions, it strikes me
14 that there are two overarching realities that will
15 permeate all of the discussions today. The first
16 overarching reality is the realization that there is
17 a great deal about the transmissible spongiform
18 encephalopathies that we don't know.

19 While we know a fair amount about the
20 TSEs, we need to know more about their pathogenesis,
21 about their transmissibility, about the inter-
22 relatedness of different TSEs, about the species
23 specificity and so on. The bottom line is that there
24 are tremendous gaps in our knowledge about TSEs.

25 The second overarching reality that will

1 permeate the discussion today is the realization that,
2 even though there are gaps in our knowledge, we at the
3 FDA have an obligation to take the most reasonable and
4 rational steps that we can to protect the public
5 health. Even given the gaps in our knowledge, we have
6 an obligation to do the most appropriate and most
7 balanced things that we can do to protect the public
8 health.

9 The challenge to the committee today is to
10 take the best information that they have and let that
11 drive them to reach the proper conclusions to best
12 protect the public health.

13 As new information is gathered in the
14 future, we'll have an opportunity to go back and re-
15 view and re-analyze the recommendations that you
16 make today, but for today you're challenged to take
17 the information that is available, to review what is
18 known about the TSEs and the processing of gelatin,
19 and to make recommendations to the FDA on the ways
20 that we can most reasonably and most rationally and in
21 the most balanced way possible protect the public
22 health.

23 To the members of the committee, to the
24 members of the general public, to our colleagues from
25 industry and from the media, to my co-workers at FDA

1 and other Federal agencies, I thank you for being here
2 today. I welcome you to this meeting of the TSEs, and
3 I wish you all the very best of luck in your
4 deliberations.

5 Thank you.

6 CHAIRMAN BROWN: Thank you, Dr. Wykoff.

7 We have next on the agenda the open public
8 hearing for any members of the public who would like
9 to make a statement concerning the matter before the
10 committee.

11 I will ask Dr. Freas to call on any
12 speakers who have requested some time to comment. I
13 would ask that, according to FDA hearing rules, that
14 any speaker who wishes to speak, limit his
15 presentation -- his or her presentation to a maximum
16 of five minutes. Dr. Freas.

17 DR. FREAS: Dr. Brown, so far I have
18 received one response to the Federal Register
19 invitation to speak in this open public hearing, and
20 that is from Dr. Thomas Higgins of Viskase
21 Corporation. Mr. Higgins, will you come to the
22 microphone at this time, please.

23 On his way to the microphone, I would like
24 to state, if there are other speakers, there will be
25 an opportunity for them to speak this morning, and we

1 do ask that everybody who addresses the committee to
2 please state any current or financial involvement that
3 you may have with any firm or product you may wish to
4 comment upon. Thank you.

5 MR. HIGGINS: My name is Tom Higgins. I'm
6 Director of Regulatory Affairs for Viskase Corporation
7 in Chicago, Illinois. Viskase Corporation is grateful
8 for the opportunity that you've given for this open
9 meeting and the opportunity to present comments.

10 Viskase Corporation manufactures food
11 packaging material, and Viskase Corporation has an
12 interest in gelatin in its end uses -- in its uses in
13 food packaging material, both edible packaging
14 material and non-edible packaging material where
15 gelatin might be in the food contact surfaces of this
16 material.

17 We do not currently manufacture any
18 products that contain gelatin, but we have from time
19 to time development projects in place, and we would
20 like to keep the option of using gelatin in food
21 contact materials and in edible materials.

22 With regard to edible collagen -- and I
23 realize that I've missed the target a bit on what
24 you're actually here to discuss, but we are also
25 interested in edible collagen. As you know, edible

1 collagen has long been used in packaging material, and
2 we sell a Genesys edible collagen film that's used to
3 wrap premium netted hams and other netted meat
4 products.

5 We have also in the past manufactured
6 edible sausage casings derived from edible collagen,
7 and this product remains a potential commercial
8 product for Viskase.

9 You are more aware than I of the reasons
10 why gelatin is BSE-free, and it's clear from the
11 opening remarks that that's the main focus of your
12 discussions today. With regard to edible collagen,
13 that is also BSE-free.

14 BSE-free cattle are the source of the
15 collagen. There is no BSE infectivity in cattle hides
16 from which edible collagen is derived, and there is
17 thorough chemical processing during the manufacture of
18 edible collagen and of the materials that are made
19 form edible collagen, such that it would tend to
20 reduce or eliminate BSE infective material.

21 Furthermore, in the final use of edible
22 collagen on meat products, there is a heat processing
23 step, either by the meat packer who makes the
24 processed meat or by the consumer before the product
25 is eaten or by both.

1 That concludes my remarks, and thank you
2 very much.

3 DR. FREAS: Thank you, Mr. Higgins.

4 Is there anyone else in the room at this
5 time who would like to address the committee? There
6 will be another open public hearing tomorrow morning.
7 Should anyone decide that they would like to address
8 the committee during the open public hearing tomorrow
9 morning, please see me during one of the scheduled
10 breaks or during lunchtime today, and we'll put you on
11 the agenda.

12 Dr. Brown, I turn the microphone back to
13 you.

14 CHAIRMAN BROWN: We now begin our
15 educational session with a talk by Dr. Kiki Hellman
16 from the Center for Devices and Radiological Health of
17 the FDA. Dr. Hellman.

18 DR. HELLMAN: Thank you, Dr. Brown.

19 Good morning to all of you. I'd like to
20 add my welcome -- No, excuse me. That's for later.
21 I'll mention when the slides are in. Thank you.

22 I'd like to add my welcome to the members
23 of the TSE Advisory Committee, the speakers, and the
24 audience, and to thank you for participating in this
25 first meeting of the committee. We certainly look

1 forward to your input.

2 I'd like the first slide, please. I would
3 also like to thank the FDA planning group, Doctors
4 Asher, Bailey, Honstead, and Vanderveen, and Ms.
5 Vincent for their considerable input to the substance
6 of the meeting, and to Ms. Gangloff, an Executive
7 Secretary to the Office of the Commissioner of FDA.

8 Excuse me. I'd like the first slide, not
9 the overhead. All right. Okay, thank you.

10 -- to Ms. Gangloff, and to Dr. Freas,
11 Executive Secretary of the TSE Advisory Committee for
12 their organizational and coordinating skills in
13 preparation for today's meeting.

14 We believe that the TSE Advisory
15 Committee, as indicated previously by Dr. Wykoff, is
16 a very important vehicle for discussing the latest
17 scientific information on transmissible spongiform
18 encephalopathies or TSEs, such as bovine spongiform
19 encephalopathy (BSE) and the potential risk of TSE
20 transmission via FDA regulated products.

21 Today I reiterate, we will focus on the
22 safety of both domestic and imported gelatin and
23 gelatin byproducts with regard to the risk posed by
24 BSE.

25 In providing an overview for the gelatin

1 issue, I'd like to first indicate the charge to the
2 committee and certain key questions for the committee
3 developed by the FDA planning group, then provide a
4 brief background of the BSE issue and the actions
5 taken by the FDA to protect public health vis a vis
6 bovine derived materials in the products that we
7 regulate; (3) discuss the use of gelatin and its
8 derivatives in FDA regulated products; (4) the
9 agency's current position on gelatin and our efforts
10 in reevaluating that position; and finally, the
11 importance of the committee's input and
12 recommendations regarding the use of gelatin.

13 The committee's charge -- and I reiterate
14 -- is to assess the safety of both imported and
15 domestic gelatin and gelatin byproducts used in FDA
16 regulated products with regard to the risk posed by
17 BSE. The primary thrust of the charge for today's
18 meeting is products for administration to humans.

19 Gelatin is currently exempt from the
20 restrictions that FDA recommends for other bovine
21 derived materials, namely, that for materials other
22 than gelatin that come from cattle born, raised or
23 slaughtered in countries where BSE is known to exist,
24 according to the USDA, not be used in the manufacture
25 of FDA regulated products intended for administration

1 to humans or animals.

2 This has been indicated in a number of
3 letters to the regulated industry beginning in 1992
4 and, most recently, in May 1996.

5 The exemption for gelatin is based on FDA
6 review of processing and manufacturing procedures for
7 pharmaceutical gelatin provided after discussions in
8 May 1994 between the FDA, the industry and the gelatin
9 manufacturing industry. Subsequently, a FDA letter to
10 legal counsel of the gelatin industry was sent in July
11 1994 and again in May 1996, indicating that FDA does
12 not object to FDA regulated products containing
13 pharmaceutical grade gelatin made from cattle from BSE
14 countries and, further, that FDA was not extending the
15 recommendations concerning material from BSE countries
16 to dairy products as well as gelatin, as indicated
17 initially in an FDA August 17, '94 letter to
18 manufacturers and importers of dietary supplements and
19 cosmetics.

20 I will indicate that the decision made by
21 the FDA at that time was based on the information that
22 we had at that time.

23 In considering their charge, there are two
24 summary questions that we would like the committee to
25 address:

1 (1) Is there sufficient scientific
2 justification to continue the exemption of gelatin
3 from the restrictions FDA recommends for other bovine-
4 derived materials from BSE countries -- that is, that
5 these materials not come from BSE countries, as
6 designated by the USDA?

7 (2) If not, what level of restriction
8 will appropriately reduce the risk:

9 Restrict gelatin from all designated BSE
10 countries?

11 Restrict gelatin from those countries
12 where BSE is prevalent? In this case, how would
13 prevalent be defined?

14 Allow gelatin from all BSE-free herds,
15 even though they may be from a BSE country? If so,
16 what controls would be needed; or provide some other
17 level of control? That is, a country's criteria for
18 identifying suspect BSE cases and overall surveillance
19 and testing systems, or use of specific inactivation
20 methods?

21 Gelatin is an animal derived material
22 that's obtained by partial hydrolysis of collagen
23 derived from the animal's skin, connective tissue, and
24 bones, either individually or collectively. The
25 animal sources most commonly used in the products that

1 we see are bovine and porcine sources.

2 Gelatin is used in biologicals, foods and
3 cosmetics, medical devices, and pharmaceuticals.
4 Since gelatin is a process material, we would like the
5 committee to consider especially processing and
6 process validation:

7 (1) What specific processing procedures
8 are essential in assuring optimum inactivation of the
9 BSE agent?

10 (2) What criteria should be considered in
11 analysis of process validation data?

12 Finally, is there one gelatin
13 manufacturing process that is superior for
14 inactivating the BSE infectious agent?

15 To provide additional background and a
16 perspective for the gelatin issue in the context of
17 BSE and FDA regulated products, it's helpful perhaps
18 to discuss BSE and the actions that the FDA has taken
19 to protect public health and safety vis a vis the
20 products that we regulate.

21 This is illustrated in the next four
22 slides. I apologize. They might be difficult to see,
23 but if you're interested in them, we can have copies
24 made for you to take home, but these slides will
25 provide a timeline or, in essence, a chronology of the

1 major FDA actions over the last ten or so years, and
2 it is not intended to be comprehensive.

3 As we are aware, BSE is believed to be a
4 transmissible, progressively degenerative neurological
5 disease of cattle similar to scrapie in sheep. Other
6 such diseases are kuru and Cruetzfeldt-Jacob disease
7 or CJD in humans, chronic wasting disease in mule deer
8 and elk, and transmissible's mink encephalopathy.

9 These disease, collectively known as TSEs,
10 are characterized by an incubation period of several
11 years during which there is no visible indication of
12 disease, a relatively short clinical course of
13 neurological signs, and eventual death. There is no
14 known treatment or cure.

15 BSE was first recognized as a new disease
16 of cattle in November 1986 by researchers of the
17 Central Veterinary Laboratory of the British Ministry
18 of Agriculture, Foods and Fisheries in Weybridge,
19 England. Epidemiological evidence established that it
20 was an extended common source outbreak. That is, it
21 occurred in many places at approximately the same
22 time, and was traced to the same source.

23 It is believed that rendered feed
24 ingredients contaminated with the TSE agent was the
25 common source of infection. This expanded when

1 carcasses of infected cattle were recycled into
2 rendered food ingredients, further spreading the TSE
3 agent.

4 Since BSE was first diagnosed in Great
5 Britain, more than 165,000 cattle from approximately
6 33,000 herds have been diagnosed with the disease, and
7 BSE has been reported in native cattle in France,
8 Switzerland, Portugal, the Republic of Ireland,
9 Northern Ireland, and the Netherlands.

10 BSE has not been detected in cattle in the
11 U.S., as reported from the surveillance and monitoring
12 program at the USDA, which has examined more than 5500
13 brains of U.S. cattle exhibiting unusual neurological
14 symptoms with no signs of TSE upon microscopic
15 histopathology examination.

16 Since 1989 no cattle have been imported
17 into the U.S. from BSE countries, as designated by
18 USDA.

19 These slides do not list the actions taken
20 by the USDA and the efforts of our sister public
21 health service agencies, the National Institutes of
22 Health and the Centers for Disease Control, which have
23 been considerable, and with whom we have worked
24 closely since the beginning of the BSE issue as we all
25 focus on better scientific understanding of BSE and

1 TSEs in general.

2 In December 1990 the first meeting of the
3 FDA BSE Task Force was held, with representatives from
4 the different FDA centers to discuss the BSE issue and
5 its impact on regulated products. Outcomes included
6 development of product inventories of bovine derived
7 materials in order to identify the scope of the
8 problem, and then guidance letters to the regulated
9 industry on products of bovine origin.

10 The Centers developed their own
11 initiatives and projects and continue to monitor the
12 situation in Great Britain. When it became clear by
13 1992 that the BSE epidemic was accelerating, the FDA
14 BSE Working Group was established in the Office of the
15 Commissioner to provide coordination across FDA
16 centers on emerging BSE issues.

17 Beginning in 1992, as I indicated, FDA
18 issued a series of letters to all manufacturers of FDA
19 regulated products requesting that bovine derived
20 materials from cattle in countries designated by the
21 USDA as countries where BSE exist not be used in the
22 manufacture of FDA regulated products intended for
23 administration to humans, and an import bulletin to
24 alert field units to imports from BSE countries of
25 animal byproducts and regulated products with animal

1 byproducts ingredients.

2 This was then followed by an import alert
3 to detain without examination shipment of high risk
4 bovine tissues and tissue derived ingredients from BSE
5 countries. The FDA also moved quickly to ban the use
6 of animal proteins in ruminant feed.

7 Scientists have theorized on the impact of
8 BSE on human health and its possible link to CJD. The
9 incidence of CJD in the U.S. is similar to that in the
10 rest of the world. Sporadic cases of CJD occur
11 worldwide at a rate of about one case per million
12 population per year.

13 On March 20, 1996, the British government
14 announced ten cases in Great Britain of a previously
15 unrecognized form of CJD and its possible relationship
16 with BSE. The Spongiform Encephalopathy Advisory
17 Committee or SEAC postulated a link between the cases
18 of variant CJD or VCJD, as it was termed, and exposure
19 to BSE infected beef, most likely before 1989.

20 In April 1996 international experts at a
21 World Health Organization consultation concluded that,
22 while epidemiologic -- while there's no definite link
23 between BSE and those with VCJD, epidemiological
24 evidence suggests that exposure to BSE before the
25 specified tissue ban of the United Kingdom in 1989 may

1 be the most likely explanation.

2 To date VCJD has been identified in 16
3 people in BSE countries, 15 in Great Britain and one
4 in France. In October 1996 Dr. John Collinge of
5 Britain and his colleagues published data suggesting
6 that the agent found in VCJD resembles the BSE agent
7 rather than that found in sporadic cases of CJD.

8 As a result of these latest findings,
9 several measures were taken by the FDA to further
10 reduce the risk of BSE occurring in the U.S., even
11 though -- and I reiterate, even though there is yet no
12 established scientific link between BSE and VCJD in
13 humans.

14 Among others, these included reinstating
15 meetings of the FDA BSE Working Group, expediting
16 regulations prohibiting ruminant protein in ruminant
17 feeds, issuing letters to manufacturers of FDA
18 regulated products alerting them to the new
19 information from Great Britain and to reiterate
20 earlier recommendations, issuing the letter to legal
21 counsel of the gelatin industry reiterating earlier
22 statements, and rechartering the CJD Advisory
23 Committee as the TSE Advisory Committee.

24 Early this year the FDA published the
25 proposed rule on the feed ban for comment and provided

1 an update on this, among other TSE related topics, to
2 the U.S. Congress. The final draft rule on the
3 mammalian to ruminant feed ban has just been published
4 for comment, and we are convening the first meeting of
5 the TSE Advisory Committee today to assess the safety
6 of gelatin and its use in FDA regulated products for
7 administration to humans.

8 Of course, we will continue to follow
9 developments in this area and take action on product
10 related concerns, as appropriate, with the help of the
11 Committee.

12 Gelatin and its derivatives, as I've
13 indicated, are used in a variety of FDA regulated
14 products, from biologicals and foods and cosmetics to
15 medical devices and pharmaceuticals.

16 May I go to the overheads, please, now?
17 I have two overheads.

18 The following list of FDA regulated
19 product areas containing gelatin or its derivatives
20 was generated from data in the individual FDA centers.
21 It serves to demonstrate the diversity of gelatin
22 applications and products.

23 Whether they be for medical use, BI
24 injectable, implantable, oral or topical
25 administration or for foods and cosmetics, biologicals

1 under the regulatory purview of the Center for
2 Biologics, Evaluation and Research range from
3 bacterial and viral vaccines to therapeutic
4 antibodies, thrombolytic enzymes, and other bioactive
5 proteins and peptides, lipids and stem cells used for
6 therapeutic purposes.

7 The Center for Food Safety and Applied
8 Nutrition data indicates that there are a variety of
9 foods containing gelatin, ranging from jellies, dairy
10 products, soups, bread and pastry products, to
11 different types of dried and frozen foods.

12 Gelatin used in cosmetics includes skin
13 creams, bath and shower products, and hair and nail
14 products. The use in foods and cosmetics seems to be
15 ubiquitous.

16 The next overhead, please.

17 The use of gelatin in medical devices
18 under the regulatory responsibility of the Center for
19 Devices and Radiological Health is primarily for
20 vascular grafts where the gelatin is coated onto a
21 synthetic material, lung patches and gelatin sponges
22 for surgical use, in addition to a gelatin film for
23 ophthalmic use.

24 The Center for Drugs Evaluation and
25 Research oversees a plethora of gelatin capsule drug

1 products for many indications, from antibiotics,
2 sedatives, analgesics, and antivirals to a wide
3 variety of over-the-counter preparations.

4 Food animal drugs and feeds under the
5 regulatory authority of the Center for Veterinary
6 Medicine utilize little gelatin except for restaurant
7 plate waste for animal feed, also food animal drugs
8 and feeds.

9 As is evident, some of these products are
10 used quite extensively, while others have a rather
11 specialized use or indication. The amount of gelatin
12 used in these products also varies and is oftentimes
13 quite a small component of the overall product. The
14 animal source, in most cases, is either bovine or
15 porcine, where it is known.

16 That's all for the overheads. Thank you.

17 Since the March 1996 announcement of human
18 cases of VCJD, the agency has been reevaluating its
19 position on gelatin. Among others, the elements that
20 have been considered in this reevaluation are:

21 (1) Material sourcing; that is, the
22 country of origin of the animal, as well as the animal
23 itself, the concern being primarily bovine sources;
24 and

25 (2) Gelatin processing and process

1 validation data, and the conclusions that can be drawn
2 from these data regarding the safety of the product
3 and its freedom from BSE contamination.

4 This afternoon there will be a detailed
5 discussion of the review issues that are considered in
6 the analysis of such data.

7 To aid FDA in this reevaluation and in
8 developing its policy on gelatin, a material that you
9 have seen is present in so many different products
10 that we regulate, we ask the TSE Advisory Committee as
11 it addresses its charge consider the following factors
12 which have been identified as agenda items for this
13 meeting:

14 (1) Issues related to sources and
15 materials used in gelatin manufacture and appropriate
16 controls, including the country of origin of the
17 animals, the country's BSE surveillance systems, and
18 the other animal controls in place;

19 (2) Gelatin processing in the context of
20 survivability of TSE agents and their inactivation
21 kinetics, along with process validation and the
22 criteria used in evaluating validation data;

23 Finally, based on these factors an
24 assessment of the level of risk of gelatin in FDA
25 regulated products.

1 In addressing this charge, the committee
2 will be performing an invaluable function,
3 contributing to a science based approach for decision
4 making on this issue to assure the continued safety of
5 FDA regulated products.

6 Thank you.

7 CHAIRMAN BROWN: Thank you very much, Dr.
8 Hellman.

9 We are, as you may imagine, already
10 running substantially ahead of schedule, and I doubt
11 seriously that anyone feels the need of a break at
12 this point. What I propose, therefore, to do is to
13 continue directly on with one or both of the following
14 two presentations and, if necessary, have an extended
15 break for lunch; but I think we will continue at least
16 with one of the next speakers.

17 The topic, broadly speaking, of the next
18 two speakers will be the sources of materials for
19 gelatin manufacture. The first speaker is Dr. John
20 Vanderveen, who is at the microphone now.

21 DR. VANDERVEEN: Thank you, Dr. Brown.

22 It was the Committee's judgment that it
23 would be useful -- the planning committee's judgment
24 that it would be useful to have a discussion of the
25 source material, raw materials, for gelatin production

1 in the United States, and probably some discussion, as
2 you'll see later, relative to the sources of gelatin
3 from other gelatin used in the United States.

4 The next slide, please.

5 In this approach to get this information,
6 we decided we would write to the gelatin manufacturers
7 of the U.S. and ask for information, and a letter was
8 sent to eight companies, this on March, by Dr.
9 Friedman. That is the source of the data that I will
10 be talking of.

11 We did have one other letter that was
12 submitted to the agency prior to that time and which
13 was also used.

14 There were three questions in this
15 request. May I have the next Vu-graph, please? The
16 first question is: What is the source, country of
17 origin, and identity of the animals and types of
18 tissues used as raw materials for gelatin manufacture
19 in the U.S. by your company?

20 Next slide, please.

21 A second question of that was: Do you
22 have veterinary inspection of the animals that are
23 used in gelatin sources?

24 Next slide, please.

25 The results of the responses from all of

1 these companies indicate that the primary source in
2 the United States is pork skins from either the U.S.
3 or Canada and, secondly, cattle hide trimmings from
4 the United States, some imported from Brazil, a very
5 small amount from the Dominican Republic, and some
6 from Argentina; cattle bones -- the main source is the
7 United States, a minor source is the country of
8 Argentina.

9 In reference to veterinary inspection --
10 next slide, please -- all U.S. source material is from
11 U.S. inspected plants, according to the companies.
12 Foreign source material is inspected by veterinarians,
13 and may I add that they included inspection of animals
14 prior to and following slaughter.

15 The next question that was asked of each
16 company -- may I have the next slide, please? -- is:
17 For retail food products, identify the source, country
18 of origin, of gelatin manufactured by your company.
19 Please indicate what portion of gelatin, if any, is
20 derived from BSE countries.

21 An answer to that is found on the next
22 slide. You will see that a number of non-BSE
23 countries were used by some of the firms, and the
24 countries are listed there: Argentina, Australia,
25 Belgium, Brazil, Columbia, Germany, Mexico, New

1 Zealand, South Africa, and Sweden.

2 Some of these countries, the U.S. firm has
3 partnerships with local companies, and they do have
4 significant role in the production of the gelatin in
5 those countries. Only one country -- Only one BSE
6 country was the source of gelatin imported by one
7 company.

8 I'd like to talk a little bit about that
9 source. The source of gelatin was primarily pork
10 skins from France, but there were some gelatin derived
11 from cattle hides. There was no indication that any
12 cattle bone was used in gelatin production in France
13 by this company or any other company, and there was no
14 other BSE derived materials used by American
15 manufacturers of gelatin.

16 The last question dealt with information
17 -- and may I have the next slide, please? --
18 information that: Does the company have any
19 scientific data to demonstrate that gelatin processing
20 results in destruction or elimination of BSE
21 infectious agents?

22 To that question, the companies
23 unanimously indicated that the only information they
24 have is that that was submitted by the International
25 Gelatin Manufacturers Association, which has been

1 submitted to the agency and is available, published.

2 May I have the last three slides then,
3 please? That's what this slide is. May I have the
4 next slide, please?

5 I'd just like to point out then the limits
6 of the information. The data only applied to U.S.
7 manufacturers of gelatin producing domestically and
8 internationally.

9 The last slide: It is fair to recognize,
10 and you will hear more information from other speakers
11 later today, that there is importation of foods
12 containing gelatin or gelatin produced by non-U.S.
13 manufacturers which is not included in this report,
14 and you will hear more about the production of gelatin
15 in other countries by non-U.S. firms later in a
16 presentation.

17 If you have any questions about this
18 information, I'll be happy to try to answer them or
19 get you an answer from the source. Thank you.

20 CHAIRMAN BROWN: Thank you, Dr.
21 Vanderveen.

22 I think we'll go right on ahead and have
23 Dr. Honstead now give us the other talk on the
24 sourcing of gelatin, and then we will have some time
25 for any member of the committee to ask questions of

1 any of the three speakers that they will have heard.

2 Dr. Honstead.

3 DR. HONSTEAD: Thank you, and good
4 morning, everybody. My comments this morning are on
5 sources of raw materials for European Community
6 members' gelatin manufacturing.

7 European Community member countries are
8 all subject to the decisions of the EC parliament, and
9 they implement these decisions in their national
10 regulations. The current status of sourcing tissues
11 for gelatin production is based on provisions of EC
12 decisions which provide that gelatin can be produced
13 from bovine materials under strict sets of processing
14 conditions and controls.

15 Another EC decision, however, specifies
16 that these source materials are first subject to the
17 specified bovine materials ban which prohibits
18 consumption of certain bovine materials by any animal,
19 including humans. These materials include the entire
20 head, the spinal column, the spleen, tonsil,
21 intestine, and thymus.

22 The hide and bones, other than the head
23 and spinal column, or the carcass are available to the
24 gelatin processing industry.

25 These decisions also apply to the United

1 Kingdom, which is considered by the EC to be the only
2 country with a high incidence of BSE. However,
3 reports by the British Ministry of Agriculture, Foods
4 and Fisheries state that no gelatin in the U.K. is
5 being produced from bovine materials sourced from
6 within the U.K.

7 FDA will continue to monitor this
8 situation, and Mr. Schrieber, a later speaker today,
9 is going to provide more information and comments on
10 these sources of raw materials later this afternoon.

11 Thank you.

12 CHAIRMAN BROWN: Well, we're only an hour
13 and a half ahead of schedule now. I think it's time
14 to break up the formality a little bit, and I have one
15 or two questions for the speakers, and I hope other
16 members of the committee may also do it.

17 I always thought that hooves were used as
18 a source of gelatin, and I wonder if this is simply a
19 misconception or whether hooves are out of fashion or
20 whether I -- What is the problem there? Either Dr.
21 Honstead or Dr. Vanderveen. A response, or anybody in
22 the industry who is a gelatin manufacturer?

23 DR. WRATHALL: Dr. Brown, my understanding
24 is that the hooves are not used. They are removed and
25 not used in the manufacture of bone for gelatin making

1 processes.

2 CHAIRMAN BROWN: Anywhere? I mean,
3 certainly, here, because you would know that.

4 DR. WRATHALL: Certainly, in those plants
5 that I visited that, I think, is the case, and I was
6 told that it was mandated that they would not be used.

7 CHAIRMAN BROWN: Is there any reason for
8 that, do you know?

9 DR. WRATHALL: I think it was primarily
10 dealing with the possible contamination from matter on
11 the hooves and that the cut would be made several
12 inches above.

13 CHAIRMAN BROWN: Yes? From the floor.
14 Would you use the microphone, please, and identify
15 yourself?

16 MR. SCHRIEBER: My name is Reinhard
17 Schrieber. I will make a speech this afternoon on
18 manufacturing in Europe.

19 I think that the answer to your question
20 is the hooves have never been used for gelatin
21 manufacturing, because the content of the --

22 CHAIRMAN BROWN: The microphone has been
23 going on and off at the speaker's position.

24 MR. SCHRIEBER: Maybe this is better.
25 Okay.

1 The reason for not using hooves is quite
2 easy to answer. Hooves have never been used to
3 manufacture gelatine, because the main protein in the
4 hooves is keratin and not collagen, and collagen, as
5 you know, is the main source, the only source,
6 basically, where you can manufacture gelatin from.

7 The misunderstanding might be that in the
8 past hooves has been used to manufacture peptones or
9 amino acids by total degradation of this protein, but
10 for gelatin manufacturing they are unusable.

11 CHAIRMAN BROWN: Thank you very much.
12 Other questions? Yes, Dr. Schonberger?

13 DR. SCHONBERGER: I just wanted a
14 clarification. Did we hear that the skulls and the
15 bone that's right near the central nervous system are
16 not used for gelatin in the United Kingdom or did I
17 mis-hear that?

18 CHAIRMAN BROWN: Dr. Honstead? Oh, Dr.
19 Vanderveen. The question involves the use of the
20 skull or bones in the skull or spinal column, the
21 vertebrae or the skull, as sources for gelatin.

22 DR. HONSTEAD: What's the question?

23 CHAIRMAN BROWN: The question is: Are
24 they excluded? They are not used?

25 DR. HONSTEAD: In the EC?

1 CHAIRMAN BROWN: Well, anywhere.

2 DR. HONSTEAD: In the EC the entire head
3 and spinal column is banned for consumption by any
4 animal.

5 CHAIRMAN BROWN: Is that just the spinal
6 column or the vertebral?

7 DR. HONSTEAD: The spinal column includes
8 all of that, the spinal cord and all the soft tissues,
9 as well as the bones.

10 In non-EC countries, of course, those
11 rules don't apply, and in the United States, of
12 course, they could use it.

13 DR. SCHONBERGER: So it's not made into
14 gelatin then, the skulls?

15 DR. HONSTEAD: No, the skulls are not used
16 in the EC, as best of my understanding. We're just
17 talking regulations here.

18 CHAIRMAN BROWN: EC, for those who don't
19 know, is the European Community. Yes?

20 DR. HUESTON: Dr. Honstead, can you
21 comment on the level of surveillance and compliance in
22 the European Community as it relates to these rules?
23 I realize and acknowledge the regulations you state
24 are accurate to the best of my knowledge.

25 DR. HONSTEAD: No. We don't have any

1 understanding of that.

2 CHAIRMAN BROWN: Dr. Schrieber.

3 MR. SCHRIEBER: Excuse me, Dr. Honstead.
4 I have to make a slight correction.

5 First of all, to give you one answer which
6 is very important, today in the United Kingdom no
7 gelatine manufacture takes place at all for
8 pharmaceutical or edible or cosmetic consumption based
9 on U.K. raw material. You will see that this
10 afternoon.

11 So there is no gelatine manufacture in the
12 moment from U.K. raw material for human consumption.
13 There's still a little bit for photographic purposes,
14 but it doesn't matter with regard to BSE.

15 A slight correction with regard to spinal
16 cord and brain: The regulation in Europe is that in
17 the U.K. it is totally banned, because it is a so
18 called SBO, specified bovine offal. It's destroyed.
19 It's incinerated.

20 The two other countries in which it is
21 banned completely by regulation is Switzerland and
22 France. Those are the two other countries where we
23 have some incidences, still at a very low level, but
24 there are incidences. The other countries basically,
25 by regulation, it's free, but you will hear a little

1 bit more this afternoon about what the gelatine
2 industry is doing.

3 CHAIRMAN BROWN: Yes, Dr. Harrell?

4 DR. SCHONBERGER: Excuse me. We knew we
5 invited the right speakers.

6 MS. HARRELL: Good morning. My name is
7 Ms. Barbara Harrell. I'm the only one that's not a
8 doctor. I'm a consumer rep, and I have two questions
9 for either one of the speakers.

10 The first one is: How long from the point
11 of infection until the test for BSE is reactive in the
12 animals, in the bovine?

13 CHAIRMAN BROWN: Any specific test you're
14 referring to?

15 MS. HARRELL: I'm not aware of a test or
16 I don't know.

17 CHAIRMAN BROWN: Okay, go ahead.

18 MS. HARRELL: No, not when they get sick,
19 but when -- As far as the testing, I don't know what
20 the test is, how it's done, a blood test or whatever.
21 At what point, or how long is it before it becomes
22 reactive after they're infected?

23 Then number two would be --

24 CHAIRMAN BROWN: Excuse me. Let me
25 rephrase your first question. Is there -- First of

1 all, is there a test to detect BSE, number one; and
2 two, if there is, at what point in the course of the
3 illness does it become positive? Is that correct,
4 what you're asking?

5 MS. HARRELL: Well, I understand that you
6 do a test for BSE. You're saying that some cattle are
7 free of it. So I would imagine --

8 CHAIRMAN BROWN: Right. Well, we'll get
9 into that.

10 MS. HARRELL: -- there is a test.

11 CHAIRMAN BROWN: Okay. We'll answer that
12 question.

13 MS. HARRELL: The other thing: If there
14 is a test, can someone respond to the specificity and
15 the sensitivity of that test?

16 CHAIRMAN BROWN: Would anybody like to
17 respond? If not, I will.

18 There is no practical test to detect BSE
19 short of doing a biopsy of the brain, possibly. Now
20 there is evidence that, if one does a biopsy of a
21 tonsil of an infected cow, it might also be positive,
22 but there's very little information about that.

23 There is no, shall we say, test tube
24 laboratory diagnostic test for BSE or any other
25 spongiform encephalopathy. If there were, it would

1 require even more study to know at what point during
2 the course of the illness it became positive.

3 There is a test which is used, if there
4 are -- if there is a very high level of infectivity,
5 and here I can back up just a bit by telling you that
6 the most sensitive test for the diagnosis of any of
7 the spongiform encephalopathies is simply the
8 inoculation of a suspect tissue into a susceptible
9 experimental animal. That is the most sensitive test.

10 There is another test which detects a
11 pathological protein which may, in fact, be the
12 causative agent itself, sometimes called the prion
13 protein, but the test detection sensitivity is
14 approximately ten to 100,000-fold lower than when you
15 actually inoculate a piece of tissue to see if the
16 tissue will transmit the disease.

17 In the context of today's discussion,
18 levels of infectivity that we are talking about would
19 never begin to approach that level of detectability in
20 which the protein could be detected and used as a
21 marker. So we are saddled, unfortunately, in this
22 field with a time consuming, expensive test which has
23 essentially no practical bearing on the issue of
24 diagnosing these diseases in cattle.

25 With that, I'll stop unless you don't

1 understand, and I can try and explain better.

2 Yes, Larry?

3 DR. SCHONBERGER: She was also interested
4 primarily in what you could use before the animal
5 became sick, and I think the answer for that is there
6 is even less ability to handle that, which is what --

7 CHAIRMAN BROWN: Exactly.

8 MS. HARRELL: Right. That's what I was
9 talking about, during the incubation period.

10 CHAIRMAN BROWN: Yes. Well, we don't --
11 Even when the animal is sick, we don't have a test
12 except the animal is sick, and we look at the brain,
13 and it looks like spongiform encephalopathy, and if we
14 look for the protein in the brain, we find it at that
15 point; and if we inoculate the brain into a
16 susceptible animal -- for example, another cow -- we
17 can transmit the disease.

18 These are all three possibilities.

19 MS. HARRELL: So the definition of a BSE-
20 free herd is one where there has been no identified
21 sick -- one animal. There's not been identified at
22 least identified sick animal. Right?

23 CHAIRMAN BROWN: I can't speak for what
24 the British consider to be a BSE-free herd, but I
25 would think that would be a common sense approach.

1 That is to say, people are not roaming the fields in
2 Britain at random, so far as I know, slaughtering
3 cattle to see whether or not a particular herd is
4 free.

5 Yes, Karen Hsiao? Dr. Hsiao?

6 DR. HSIAO: Paul, in some of the materials
7 that we've received prior to this meeting,
8 particularly your chapter on human -- causes of human
9 spongiform encephalopathy, there was a table that
10 lists all of the host tissues that had been used for
11 infectivity studies, and it's a beautifully put
12 together table; but --

13 CHAIRMAN BROWN: It's also out of date.

14 DR. HSIAO: -- I don't see skin or hide on
15 this table, and I wondered whether you've come across
16 any new information about skin or hide.

17 CHAIRMAN BROWN: I haven't. I'd be glad
18 to know if anybody else has. That table,
19 incidentally, that Dr. Hsiao refers to was simply a
20 listing in the natural hosts of three spongiform
21 encephalopathies, the human variety, scrapie in sheep,
22 and BSE in cattle.

23 All of the tissues that had been tested in
24 cattle at the time that that table was made up, the
25 evidence for infectivity or its absence was very

1 anecdotal. It is now much more complete, and may
2 include -- may include now, and probably does, skin.

3 To the best of my knowledge, nobody has
4 ever looked at the skin from a scrapie infected sheep,
5 and certainly they have not from a human being
6 infected with Creutzfeldt-Jakob disease.

7 We have Dr. Rohwer wanting to modify that.
8 Dr. Rohwer.

9 DR. ROHWER: There is a single report that
10 I'm aware of. It comes from the very early work on
11 scrapie by Stamp in which he -- There is a single
12 report that comes from the very early work of Stamp,
13 one of the first investigators of scrapie disease in
14 a systematic experimental way, in which he claims to
15 have inoculated skin from infected sheep into other
16 sheep, and I don't remember the numbers. They weren't
17 large, but four or five sheep that were tested did not
18 come down with any disease from this inoculation.

19 I've always been curious as to how he did
20 this technically. There is no description of how he
21 homogenized the hide or introduced it into these
22 animals, but I believe that's the only thing out
23 there.

24 CHAIRMAN BROWN: Am I correct, Bob, in
25 having said that I think, amongst tissues that are

1 under current investigation in England for BSE, skin
2 has been included?

3 DR. ROHWER: I'm not aware that it has,
4 again for technical reasons. It's not easy to
5 inoculate skin.

6 CHAIRMAN BROWN: I think the bottom line,
7 Dr. Hsiao, is that there is essentially no information
8 on skin, aside from that one study.

9 DR. ROOS: Yes, Paul, but there is WHO
10 report, March 24-26, and on the back it says relative
11 scrapie infectivity titers in tissues and body fluids
12 from naturally infected sheep and goats with clinical
13 scrapie.

14 There's a little footnote of three, which
15 is a bad Xerox here, and I can't quite see it; but I
16 think there must be some data that was compiled. In
17 fact, no detectable infectivity, category four, lists
18 cartilaginous tissue, connective tissue, skin.

19 There's a footnote 4 which reads, "No
20 infectivity was transmitted in bioassays involving
21 inoculation of up to 5mg of tissues into rodent
22 brains." So there is some data that probably --

23 CHAIRMAN BROWN: My understanding of that
24 table is that it's a composite, and it may well not be
25 completely accurate, and it may not have to do with

1 skin.

2 DR. ROOS: One last point: I guess the
3 natural transmission of scrapie is still unknown, and
4 at one point people did hypothesize that probably
5 scraping fur on wires or fence posts might be
6 important in transmission, and I don't know whether
7 there was ever any data to support that hypothesis,
8 but that might also have to do with blood and also
9 more subcutaneous tissue.

10 CHAIRMAN BROWN: Yes? Dr. Wolfe?

11 DR. WOLFE: I want to first raise a
12 general issue which is sparked off by two comments a
13 few minutes ago, and then a question about the source.

14 The general issue is that, as one looks
15 for, as I have read through a lot of this information,
16 some published/unpublished, there is a remarkable
17 plethora of studies using three animals, five animals,
18 seven animals, upon which conclusions have been made
19 that there is no infectivity.

20 For instance, just talking about this
21 category 4 in the WHO report where no detectable
22 infectivity -- we don't have any numbers as to in how
23 many animals 5mg of tissue were injected
24 intracerebrally. So I just caution us, when we reach
25 any conclusions, to ask questions about (a) how many

1 animals were involved and, if possible, -- some of
2 this has been done, some hasn't -- what are the upper
3 bounds, the 95 or 99 percent confidence intervals.

4 In an experiment with five animals, it's
5 negative, does that still mean that we could have as
6 many as ten or 20 percent animals infected, because of
7 the limits statistically of a small sample like that?
8 So a lot of problems, because a lot of these studies
9 that I've looked at are with very small numbers of
10 animals.

11 The specific point was that Dr. Hellman
12 mentioned that the sources of gelatin are (a) skin,
13 (b) bones, and (c) connective tissue. Is the source
14 of the connective tissue mainly the hide or are there
15 other sources?

16 Then the correlated question was that a
17 couple of months ago an issue was made a la U.S.
18 Department of Agriculture with respect to the
19 preparation of what I and others would call junk meat,
20 which is taking bones and stripping off protein,
21 usually lousy protein, and then making meat out of it,
22 throwing it into sausages and hotdogs and so forth.

23 What was found was that, when they
24 switched to a mechanical process for this, that in a
25 number of the samples there were elements of spinal

1 cord and neural tissue there.

2 So that my question here is: When we're
3 talking about bones, what is the assurance, if any,
4 that bones do not include neural tissue which itself,
5 obviously, does have a high problem of -- a large
6 problem of infectivity? It's a question for those who
7 are talking about making gelatin from bones.

8 CHAIRMAN BROWN: Right. Dr. Hellman?

9 DR. HELLMAN: To the best of our
10 knowledge, most of the gelatin sourcing is from hide,
11 perhaps bones, and we'll hear this afternoon from the
12 European Community, because we have some questions
13 ourselves as to what extent bones are used in the
14 European Community, and if there is discrimination
15 among the types of bones that are included.

16 One concern that we should be aware of is
17 that, if bones are crushed and they're all put
18 together in a big bag, if you will, it's going to be
19 very difficult to tell the difference between a skull
20 bone from a leg or whatever. So the bone source does
21 concern us, and also the way that the hide is
22 prepared.

23 So slaughter is a very, very important
24 element here, when we consider the sourcing.

25 DR. WOLFE: And the other question was:

1 Did you imply anything beyond -- When you said that
2 connective tissue was a source, what were you meaning
3 by that?

4 DR. HELLMAN: That was just included for
5 completeness. To the best of our knowledge, it's
6 primarily hide. So I don't think that's a concern.

7 CHAIRMAN BROWN: Dr. Hsiao.

8 DR. HSIAO: I just wanted to make another
9 comment, which has to do with species barriers. When
10 an inoculation is performed between two animals of the
11 same species, there's a much greater likelihood that
12 the host or the recipient will get infected.

13 So if you take like a mouse with scrapie
14 and you inoculate into a mouse, then there's a much
15 greater likelihood that the recipient mouse will get
16 infected, because they're the same species; but if you
17 take a sheep with scrapie and you inoculate into a
18 mouse, there's a much lower likelihood, because of the
19 so called species barrier.

20 Up until now, we've always thought that
21 the species barrier was caused by differences in the
22 amino acid sequence of the prion protein between the
23 recipient host and the animal from which the inoculum
24 was derived. What's been very puzzling about this BSE
25 phenomenon is that the amino acid difference between

1 a cow prion protein and a human prion protein is the
2 same as the amino acid difference between a sheep
3 prion protein and the human prion protein.

4 So there should have been, if you just
5 used that as a criterion, the same degree of a species
6 barrier. We've never encountered any evidence,
7 scientifically or epidemiologically, that sheep prions
8 could cross the species barrier going from sheep into
9 primates or humans.

10 It's actually the current scientific
11 understanding of prions -- or these transmissible
12 encephalopathy agents does not explain why cow prions
13 crossed over the species barrier, if they did, into
14 humans.

15 So I just wanted to point that out.
16 Therefore, when we talk about pork hides which, as far
17 as I know, first of all, they haven't -- nobody has
18 ever reported a paper with prion disease -- and then
19 again there's another species involved, and whether or
20 not that species could have the ability to cross the
21 species barrier into humans is yet another question;
22 but it seems to me right now that a pork hide would be
23 probably extremely safe.

24 Then talking about cow hides one has to
25 wonder, first of all, whether there are any prions in

1 the skin of a cow. It seems to me that no one has
2 actually done that experiment properly. Also, no one
3 has ever done the experiment where they took a mouse
4 skin from a mouse that had scrapie and inoculated a
5 mouse skin into a mouse brain, which probably would be
6 useful to know the answer to, or a sheep hide and
7 taking that and inoculating into a sheep brain, which
8 would also be useful to know the answer to.

9 Since we don't know these answers, a lot
10 of these questions are very hard to come up with
11 definitive policies for.

12 CHAIRMAN BROWN: To add something to what
13 Dr. Hsiao just said, there is, of course, a relative
14 species barrier, but it is never absolute -- that is,
15 almost never absolute. It inhibits the transmission
16 of disease between species, but it does not prevent
17 it.

18 For example, scrapie infected sheep in
19 competent hands, when inoculated, if the brains are
20 inoculated into mice, will produce scrapie in the
21 mouse on first passage in close to 75 percent of the
22 animals. It is more difficult than if one takes
23 scrapie in a sheep and inoculates it into a sheep.
24 That's correct.

25 So it's not an absolute barrier. It's a

1 partial barrier, and it does make it more difficult to
2 transmit disease, and it's one of the things that we
3 are counting on with respect to BSE in humans.

4 I think Dr. Wolfe's critique on both
5 counts was very appropriate. As a little added
6 comment about the possibility of nervous system
7 contaminating non-nervous system tissues, it is
8 traditional, at least in England, when a cow is
9 slaughtered to halve the cow with a cutting
10 instrument, usually a saw, and that saw goes directly
11 through the spinal cord.

12 You can imagine that a great deal of
13 contamination, potential contamination, might occur in
14 muscle which had been taken from cows so slaughtered.
15 So our initial reluctance to accept the possibility
16 that muscle from a BSE infected cow could infect
17 humans was probably misplaced.

18 If humans have, in fact, been infected
19 with BSE, it is more likely that the source of the
20 infection actually was nervous tissue contamination.
21 That's one point.

22 The second point is that you are
23 absolutely right in terms of the numbers of animals
24 that have been used in many cases for the detection of
25 the infectious -- My microphone is now going off, I

1 think -- the detection of the infectious agent, such
2 that a positive is very significant, but a negative
3 may not be.

4 One generally, because of the length of
5 time it takes to transmit the disease in experimental
6 animals, we don't have information based on 50 or 100
7 or 1,000 animals which, if all were negative, would be
8 very persuasive. Very often, as you say, it amounts
9 only to -- I think we may have to take an early break
10 after all.

11 DR. WOLFE: Sounds like a saw.

12 CHAIRMAN BROWN: Right. But that point is
13 well taken.

14 (Whereupon, the foregoing matter went off
15 the record at 10:17 a.m. and went back on
16 the record at 10:38 a.m.)

17 CHAIRMAN BROWN: Ladies and gentlemen,
18 could we reconvene the meeting now.

19 We're going to keep on pushing ahead, and
20 the next two presentations will concern not sourcing
21 but processing of gelatin, and we shall hear from
22 representatives of two different gelatin
23 manufacturers. Either Dr. Wrathall or Dr. Dunn, it's
24 your choice. All right, Dr. Wrathall, who is in fact
25 scheduled to be first, will now talk about processing.

1 Dr. Wrathall.

2 DR. WRATHALL: Dr. Brown, I want to thank
3 you and this committee for the opportunity to speak on
4 behalf of the Gelatin Manufacturers Institute of
5 America about the gelatin manufacturing process.

6 My name is Dr. Donald P. Wrathall. I'm a
7 Senior Technical Associate with Eastman Gelatine
8 Corporation and have worked at Eastman Gelatine for
9 the past 13 years, mainly in the area of research and
10 development, but also have some experience in the
11 analytical testing on the product side of the
12 business.

13 My topic will be limed bone gelatin or
14 limed ossein gelatin, but I'd like to start by making
15 some general comments about gelatin, if I could have
16 the next slide, please.

17 Gelatin is a pure protein obtained by the
18 partial hydrolysis of collagen derived from the skin,
19 white connective tissue and bones of animals. There
20 are two major types of gelatin. Type A is gelatin
21 derived from an acid-treated precursor such as pigskin
22 gelatin. Type B is gelatin derived from an alkali-
23 treated precursor such as limed ossein gelatin.

24 Next slide, please.

25 In the Gelatin Manufacturers Institute of

1 America, there are a variety of both types of gelatin
2 manufacturers. Type A reports gelatin manufacturers
3 are Cangel of Canada, DynaGel, Hormel Foods
4 Corporation, Kind & Knox Gelatine, Kraft Foods,
5 Atlantic Gelatin, and Systems Bio-Industries of the
6 U.S., and Leiner Davis of Mexico.

7 Type B gelatin manufacturers are Eastman
8 Gelatine Corporation and Kind & Knox Gelatine produce
9 limed ossein gelatin, and Kraft Foods Atlantic Gelatin
10 produces alkali bovine hide gelatin.

11 Next slide, please.

12 As has been mentioned previously, the most
13 common pharmaceutical uses of gelatin are in the
14 production of hard and soft capsules in vitamin
15 encapsulation and tableting.

16 Next slide, please.

17 Gelatin is also vital to the photographic
18 industry where it is used in emulsion preparation,
19 coating and hardening in virtually every photographic
20 product, including black and white photo paper, color
21 photo paper, graphic film, color film, and sensitive
22 X-ray films.

23 The primary source of photograph gelatin
24 comes from the limed ossein process, and the highest
25 possible purity is essential to meet both the

1 pharmaceutical and the photographic requirements.

2 Next slide, please.

3 The amino acid composition of gelatin is
4 virtually identical to the amino acid composition of
5 collagen, which is the major protein component of
6 bone, hide and pigskin. Of particular note is the
7 high level of proline and hydroxyproline which is a
8 common feature of both collagen and gelatin.

9 Next slide, please.

10 Some of the major functional properties of
11 gelatin are its ability to form set gel, gelation
12 properties. It's a very good emulsifier. Also the
13 aeration, stabilization properties, binding, finding,
14 encapsulation, and microencapsulation properties are
15 excellent.

16 Next slide, please.

17 Some general characteristics of Type A and
18 Type B gelatin are shown here. The final pH is
19 slightly lower for the Type A gelatin, ranging from
20 four and a half to six, compared to five to seven.

21 The isoelectric points of Type A and Type
22 B are quite different, and this is related to the
23 hydrolysis procedures. For Type A it primarily on
24 acid hydrolysis, and Type B includes both acid and
25 alkali or limed hydrolysis, which results in a much

1 lower isoelectric point.

2 The gel strength and viscosity are very
3 similar in the two gels, and the ash is also quite
4 similar in both types.

5 Next slide, please.

6 There are two major objectives in the
7 manufacturing process for gelatin. The first is
8 hydrolysis, and it is very important to hydrolyze a
9 sufficient number of cross-link and peptide bonds in
10 the three-dimensional collagen matrix in order to
11 render the hydrolyzed collagen highly soluble in
12 aqueous solutions, aqueous environments.

13 This hydrolysis is done through extensive
14 alkaline conditioning for the Type B gelatins, plus
15 acidic and thermal hydrolysis procedures for both Type
16 A and Type B gelatins.

17 The second major objective of the
18 manufacturing process is purification. This is done
19 by removing soluble proteins and other organic
20 impurities during the pre-treatment stages when the
21 collagen is still insoluble by using agitation or
22 washing and frequent solution changes.

23 Secondly, in the extraction phase
24 insoluble proteins and other insoluble organics are
25 left behind in what is termed in the industry as

1 tankage following the aqueous extraction stage. In
2 addition, filtration, deionization are also used as
3 important purification steps.

4 Next slide, please.

5 This is a schematic which demonstrates the
6 many discrete steps used in the manufacturing process
7 for both limed ossein and alkali-treated cattle and
8 pigskin process.

9 Today I will describe the limed ossein
10 process. That begins with the degreased, dried and
11 crushed cattle bones.

12 Next slide, please.

13 In the United States 98 percent of the
14 bone comes from USDA inspected plants, two percent
15 from Argentina. During the process, bone is crushed
16 to a maximum size of 5/8 inch. It is then cooked for
17 15-45 minutes at temperatures ranging between 180-250
18 degrees Fahrenheit.

19 High speed industrial centrifuges are used
20 then to remove most of the liquid tallow and the
21 water. After that, the bone is dried at an average
22 residence time between 30 and 60 minutes, and at a
23 temperature between 160 degrees and 220 degrees
24 Fahrenheit.

25 The final moisture content of the bone

1 after the drying process will typically range between
2 six and nine percent. Following the drying, a
3 separation is carried out, mainly to remove the
4 smaller pieces of bone, and the remainder have a size
5 range between 1/8 and 5/8 of an inch.

6 Another important step in the degreasing
7 process is a density separation which is carried out
8 and which concentrates and collects the high density
9 bone pieces for gelatin manufacture.

10 As a result of this process, the final
11 bone quality has a relatively high mineral to protein
12 ratio of about two. The size ranges, 1/8 to 5/8 of an
13 inch. The moisture content, 6 to 9 percent.

14 There is a sinew-tendon-ligament content
15 of approximately zero to four percent in this final
16 product, and the fat content of the bone at this point
17 ranges between one and four percent.

18 Next slide, please.

19 The degreased dry gel bone is shipped to
20 the gelatin manufacturing sites for further
21 processing, and the first step at these sites is
22 acidulation in which the bone is demineralized. Just
23 as a point of terminology in the trade, the
24 demineralized bone is termed as ossein.

25 This demineralization is carried out with

1 hydrochloric acid at a concentration of between four
2 and six percent. The acidulation time is five to
3 seven days. It takes approximately two days for the
4 bulk of the mineral to be removed, and as a result of
5 the counter-current process, the ossein is in contact
6 -- the demineralized ossein is in contact with the
7 acid for approximately three to five days.

8 The acidulation temperature ranges between
9 50 and 65 degrees Fahrenheit. Following the
10 acidulation and demineralization, the ossein is washed
11 using multiple batch or continuous rinse over a 24-
12 hour time period to remove acids, salts, fat and other
13 impurities. There's a major reduction in the residual
14 fat content as a result of this step.

15 The purpose of the acidulation is to
16 remove the mineral content of the bone, also to
17 hydrolyze some of the collagen bonds and to remove
18 non-collagen impurities.

19 Next slide, please.

20 The next step is termed the liming
21 process. In this step the ossein is pumped into
22 liming pits, and lime slurry is added at a
23 concentration of one to four percent. At this
24 concentration, there is a saturated solution of lime,
25 and it is maintained as a saturated solution

1 throughout the process.

2 As a result, the lime slurry pH ranges
3 from 12.0 up to 12.7. The time is extensive, ranging
4 from 35 to 70 days, and the liming temperature is
5 maintained between 50 and 70 degrees Fahrenheit.

6 There is daily, vigorous agitation that is
7 used during this part of the process, and at least
8 weekly lime slurry changes are made. This is -- A
9 major part of the bond hydrolysis occurs in this stage
10 of the process, and it's also a major purification
11 part of the process as well. The purpose is to
12 extensively hydrolyze collagen bonds and remove non-
13 collagen impurities.

14 Next slide, please.

15 The following step is the washing and
16 neutralization step. The ossein -- limed ossein is
17 pumped into wash mills, and there's an extensive wash
18 procedure that takes place that goes over a period of
19 24-48 hours.

20 During this procedure, very vigorous
21 agitation is used throughout the procedure, throughout
22 the washing procedure, and a large quantity of water
23 is used in this wash process, ranging between 50 and
24 100 pounds of water per pound of gelatin.

25 Water temperature ranges between 45 and 70

1 degrees Fahrenheit. At some point in the washing
2 process, mineral acid is added to neutralize excess
3 lime. This then generally brings the pH down to about
4 three, and as that acid is washed out, the pH will
5 rise back to the aim, which is generally an aim of pH
6 between five and seven for the ossein at the end of
7 this process.

8 The purpose of the washing step is to
9 remove and neutralize excess lime and to remove non-
10 collagen impurities.

11 Next slide, please.

12 Following the washing process, the gelatin
13 is pumped -- or the ossein -- Excuse me -- the ossein
14 is pumped into extraction kettles for a series of hot
15 water extractions, and again a note of terminology.
16 At this point the material extracted from the ossein
17 is termed gelatin. Demineralized water is used during
18 this extraction process.

19 The procedure is to carry out a series of
20 extractions at successively higher water temperature,
21 with the water temperature ranging from 120 degrees
22 Fahrenheit up to 200 degrees Fahrenheit. The
23 conditioning time of the water and the ossein ranges
24 from one to six hours per extraction.

25 Because of the extraction time and

1 temperature, extensive additional thermal hydrolysis
2 of the ossein bonds occurs in this state of the
3 process.

4 The main purposes of the extraction
5 process is to solubilize hydrolyzed collagen and also
6 to exclude nonextractable impurities such as fatty
7 acids, insoluble proteins. At this point, a great
8 majority of fatty acids that remain in the ossein are
9 left behind in the tankage.

10 Next slide, please.

11 Following the extraction procedure, the
12 liquid gelatin solution goes through a number of
13 additional finishing steps. The first of these is an
14 initial filtration, and a cellulose -- combination
15 cellulose/diatomaceous earth filter is used in this
16 procedure.

17 Following the filtration, the gelatin is
18 deionized sequentially through an anionic and cationic
19 resin bed. Following deionization, the gelatin is
20 concentrated using one or two steps of evaporation to
21 a concentration between 15 and 45 percent.

22 Following evaporation, the concentrated
23 gel is filtered through a polishing filter, again with
24 a cellulose/diatomaceous earth combination filter.
25 Then the pH is adjusted, usually with caustic, to a

1 final aim of between five and seven.

2 Immediately before setting and drying, the
3 gel is sterilized by heating the gelatin solution to
4 a temperature of between 280 and 290 degrees
5 Fahrenheit for eight to 12 seconds. Then the gel is
6 cooled, set and noodled, and goes on to drying beds,
7 moving drying beds through a series of chambers where
8 it is dried with highly filtered air, starting at low
9 temperatures up to -- starting at about 80 degrees up
10 to 160 degrees in the final chambers, drying chambers.

11 The final moisture content is 10-12
12 percent. Drying time ranges between one and three
13 hours.

14 Following the drying stage, the gelatin is
15 ground to an 80 to 30 mesh size. For those that may
16 not be familiar with that terminology, it's between
17 600 and 2400 micron size.

18 The finished gelatin is then tested using
19 a wide variety of microbiological, chemical and
20 physical tests. Gelatin used for photographic
21 purposes must also pass a number of highly sensitive
22 photographic tests.

23 Mr. Chairman and Committee members, that
24 concludes my presentation. Thank you.

25 CHAIRMAN BROWN: Thank you very much, Dr.

1 Wrathall. Dr. Dunn, do you have a subject which would
2 be appropriate to delay questions for the two of you
3 together or is your subject going to be substantially
4 different, so we should ask questions now?

5 DR. DUNN: I'd say more similar than
6 different.

7 CHAIRMAN BROWN: Okay, let us then go
8 right on to Dr. Dunn, and following Dr. Dunn's
9 presentation we will open the floor to questions.

10 DR. DUNN: My name is Michael Dunn. I'm
11 currently Manager of Edible and Technical Services at
12 Kind & Knox Gelatine in Sioux City, Iowa.

13 I would like to thank the FDA Planning
14 Committee for giving me the opportunity to describe --
15 Could you put the first slide on, please? I'd like
16 to thank the Committee for giving me the opportunity
17 to describe the pork skin gelatin manufacturing
18 process on behalf of the GMIA companies.

19 The GMIA pork skin gelatin producers
20 include Cangel which is based in Canada, and Leiner
21 Davis which is located in Mexico. The remainder of
22 the companies are located in the U.S., and these
23 include DynaGel, Hormel, Kind & Knox, Atlantic
24 Gelatine and SBI.

25 I will preface my presentation today by

1 making it clear that the information I will be
2 providing today represents a pooled composite of what
3 I have obtained from the member companies regarding
4 specific processing conditions and is intended to be
5 a broad representation of how the U.S. industry
6 produces pork skin gelatin, rather than a typical
7 example of how an individual company would produce the
8 product.

9 Before I describe the process, I would
10 like to make some general remarks about some of the
11 typical chemical and physical properties of pork skin
12 gelatin and its applications in the food and
13 pharmaceutical areas.

14 Could I have the second slide, please?

15 The typical pH range for pork skin gelatin
16 is about four and a half to six, which is a little
17 lower than that observed for bone gelatin. This
18 difference is driven by primarily varying customer
19 requirements for these types of gelatin.

20 The isoelectric point for pork skin
21 gelatin is distinctly higher than that observed for
22 bone gelatin, since both asparagine and glutamine are
23 preserved during the pork skin gelatin process. The
24 gel strength and viscosity, which are important
25 characteristics for the processing and the performance

1 of the finished product application, vary broadly and
2 correlate with the average molecular weight of the
3 gelatin proteins.

4 The ash varies from close to zero to as
5 high as two percent, and this depends primarily on
6 processing conditions, raw material sources, and
7 whether or not ion exchange is used.

8 Could I have the next slide, please.

9 From a nutritional standpoint, gelatin is
10 virtually all protein from a macromolecular point of
11 view, about 98-99 percent on a dry basis. Gelatin is
12 devoid, therefore, of fat and carbohydrate.

13 Other than protein, the finished gelatin
14 is composed primarily of moisture and a small amount
15 of ash.

16 Could I have the next slide, please.

17 The majority of pork skin gelatin is
18 supplied to the edible marketplace and is used in a
19 broad variety of applications, in dairy products such
20 as yogurts, cream cheeses and ice cream, in frozen
21 foods as a stabilizer, in a broad variety of gelatin
22 desserts, in confections such as Gummi Bears and
23 marshmallows, and in many other products.

24 Could I have the next slide, please.

25 Pork skin gelatin is also used in a number

1 of important pharmaceutical applications. Its primary
2 use continues to be for the manufacture of hard and
3 soft capsules. A newer and growing application is its
4 use in gelcaps or caplets. It is also used in to
5 encapsulate vitamins, flavors and colors.

6 I would also like to note that, to the
7 best of our knowledge, the gelatin used in the U.S.
8 for vaccines and surgical sponges is exclusively
9 derived from porcine sources.

10 Could I have the next slide, please.

11 In contrast to the bone gelatin process,
12 the pork skin process is much shorter in duration.
13 Since we are not starting with the hard tissue, we
14 must not -- we avoid demineralization and do not
15 employ the extensive liming process.

16 As a result, pork skin gelatin can be
17 manufactured in two to four days from start to finish.
18 In addition to the pork skins which are the source of
19 collagen protein, there is a significant amount of
20 acid used for conditioning the skins and a large
21 amount of water which is used for rinsing following
22 pre-treatment and for the extraction of gelatin.

23 There is a series of processing steps
24 which allows for the isolation and purification of
25 gelatin from this collagen containing raw material.

1 There is initially a size reduction step, which we
2 refer to as chopping, which is followed by acid
3 treatment and washing.

4 The conditioned material is then extracted
5 with hot water, and the resulting gelatin solution is
6 exposed to filtration and ion exchange. The dilute
7 gelatin solution is then concentrated, using either
8 vacuum evaporation or ultrafiltration, to produce a
9 thicker gelatin solution.

10 The thick liquor is then exposed to HCST
11 sterilization conditions. The concentrate is then
12 chilled to the gel point and extruded as noodles and
13 is dried and ground to produce a finished gelatin
14 extract.

15 Could I have the next slide, please.

16 Pork skin is the predominant raw material
17 source for the production of gelatin in the United
18 States. The pork skins that are used for the
19 production of gelatin are obtained from USDA and
20 Canadian Department of Agriculture inspected meat
21 processing plants.

22 Clean pork skins trimmed of fat, flesh and
23 hair are received fresh under refrigerated conditions
24 or frozen. The pork skins are stored under
25 refrigerated conditions until they are used for

1 gelatin production.

2 Could I have the next slide.

3 The first step in the processing of the
4 raw material involves the reduction of the size of the
5 skin material by mechanical means. The refrigerated
6 pork skins are conveyed into a piece of equipment
7 called a chopper, which cuts the skins into smaller
8 pieces.

9 As a result of this type of treatment, the
10 size of the skins is reduced from approximately one to
11 two square feet to approximately four to 24 square
12 inches. The resulting smaller pork skin pieces
13 provide for improved material flow, reduced clumping
14 of skins, and more uniform conditioning with acid as
15 a result of their increased surface area.

16 Could I have the next slide, please.

17 The skins are then transferred to large
18 tanks equipped with tumblers for agitation where they
19 are soaked at a low pH to promote swelling of the raw
20 material and to initiate the process of hydrolysis,
21 which helps to facilitate the extraction of gelatin.

22 The skins are typically held for five to
23 16 hours at a pH ranging between one and 3.8.
24 Sulfuric acid is the most commonly used, but HCL is
25 also used in some cases.

1 Following the acid treatment, skins are
2 washed with water to allow for the removal of grease,
3 acids and salts, and to adjust the pH for the
4 extraction process. A continuous rinse will take
5 between four to eight hours, and batch rinsing will
6 take anywhere from 20 to 48 hours to achieve the
7 higher pH for extraction. The pH target for
8 extraction will vary between a pH of 3.0 and 5.0.

9 Could I have the next slide.

10 The acid conditioned skins are then
11 transferred to large steam-jacketed cooking vessels
12 where they are exposed to a series of hot water
13 extractions with varying time/temperature profiles.
14 The pH, temperature, time and the number of
15 extractions employed varies across the industry and
16 depends on a number of factors, including product
17 needs, types of equipment, timing of operations, and
18 economics.

19 The number of extractions can vary between
20 three and six, but four is the most common. The
21 extraction conditions representative of the industry
22 are shown there on the slide.

23 As can be observed from this table, the
24 extraction temperature is gradually increased with
25 subsequent extractions. Remember, the temperature

1 ranges are quite broad, because they represent the
2 variability across the industry.

3 The concentration of the extracted gelatin
4 ranges between two and seven percent. This dilute
5 gelatin is referred to as the thin liquor. The
6 initial extracts which are produced at relatively
7 lower temperatures exhibit higher molecular weights,
8 viscosities, gel strengths, and are the least colored.

9 In contrast, the latter extracts, which
10 are produced at higher temperatures, exhibit lower
11 molecular weights, viscosities, gel strengths, and a
12 greater degree of color.

13 After the last extraction, the major
14 grease fraction is removed from the cooking vessels
15 and is subjected to further processing.

16 Could I have the next slide, please.

17 Subsequent to extraction, there is an
18 initial filtration step. A typical example of a
19 filtration unit would be a vertical leaf-type filter
20 that is precoated with diatomaceous earth and/or
21 cellulose.

22 This step removes coagulated protein,
23 primarily non-collagenous type, and other undissolved
24 particulate and grease. As a result, the clarity of
25 the product is improved, and the ion exchange columns

1 are protected.

2 The filter ratings with respect to pour
3 size with depend on how the filter is configured and
4 can vary between a few microns and approximately 100
5 microns.

6 Could I have the next slide, please.

7 When ion exchange is employed, it is used
8 immediately following filtration. Both anion and
9 cation exchange columns are employed to reduce the ash
10 content of the final product to within .1 to 1.1
11 percent range.

12 The conductivity of the deionized liquor
13 typically ranges between 50 and approximately 300
14 micromoles. The primary cations that are removed
15 include calcium, magnesium and iron. The major anion
16 removed will be a counter-ion of the acidulating acid,
17 sulphate in most cases, but sometimes chloride.

18 Could I have the next slide, please.

19 Vacuum evaporation is the most common
20 means of concentrating the thin liquor, although
21 ultra-filtration is used to some extent in the
22 industry. Both multiple effect rising film as well as
23 multiple effect plate and frame evaporators are used
24 in the industry.

25 The resulting thick liquor will range in

1 concentration between 15 and 35 percent gelatin,
2 depending on the type of concentration equipment
3 employed.

4 The temperature of the resulting thick
5 liquor will typically range between 113 and 150
6 degrees Fahrenheit.

7 Could I have the next slide, please.

8 Filtration is used again following the
9 concentration to clarify the gelatin liquor by
10 removing any additional coagulated protein and any
11 other particulate matter.

12 Plate and frame filtration is typically
13 used at this stage of the process, primarily because
14 of the higher viscosity of the solution. A typical
15 configuration would be a cellulose -- would be using
16 cellulose filter pads coated with diatomaceous earth.

17 Again, filter ratings will vary depending
18 on the exact configuration of the filter media. The
19 temperature typically ranges between 113 and 140
20 degrees Fahrenheit at this stage of the process.

21 Could I have the next one, please.

22 Final pH adjustments are typically
23 performed at this stage to target the pH of the final
24 product. The pH of the final product ranges between
25 three and a half to six, and is determined primarily

1 by the customer requirements.

2 Acids and bases typically used to adjust
3 pH at this point are sulfuric and hydrochloric acid.
4 Bases are sodium hydroxide and ammonium hydroxide.

5 Could I have the next slide, please.

6 The thick liquor, in most cases, is
7 further concentrated by employing a scrape surface,
8 thin film vacuum evaporator to achieve a final gelatin
9 concentration ranging between 25 and 50 percent.

10 The concentration of the gelatin solution
11 obtained at this stage is extremely dependent on the
12 viscosity of the extract, i.e., much higher
13 concentrations can be achieved with the latter
14 extracts that exhibit much lower viscosities.

15 The evaporator output temperature ranges
16 between 118 and 125 degrees Fahrenheit.

17 Could I have the next one, please.

18 All companies in the GMIA group have
19 incorporated sterilization step into their processes.
20 Stem injection or infusion is the most common form of
21 sterilization used, although the plate type is also
22 used to some extent.

23 A fully concentrated gelatin liquor is
24 exposed to sterilization temperatures ranging between
25 248 and 303 degrees Fahrenheit for up to five to 13

1 seconds to ensure microbiological purity.

2 Next slide, please.

3 The thick gelatin liquor is then chilled
4 to approximately ambient temperature employing a
5 glycol cooled votator heat exchanger tube. The
6 gelling mass is then extruded through a perforated
7 head as noodles onto a continuous oscillating conveyor
8 belt which supplies the dryer.

9 The noodles are approximately one to two
10 feet in length and about 1/8 inch in diameter. This
11 gelled form provides for maximum surface area and thus
12 efficient drying.

13 Next slide, please.

14 The wet noodles are deposited onto a
15 stainless steel, open weave drying belt that is about
16 12 feet wide and approximately 100 feet long. The
17 porous bed of noodles passes through seven to 12
18 drying zones, ranging in temperatures from 85 degrees
19 Fahrenheit in the initial zone to up to 158 degrees in
20 the final zone.

21 The temperatures of the zones gradually
22 increase as the noodles move slowly through the dryer
23 to avoid melting and the case hardening of the noodle
24 surface. Transit time through the dryer ranges
25 between two and four hours.

1 The gelatin is dried to a moisture content
2 of eight to 12.5 percent, utilizing dehumidified and
3 filtered air. At the end of the dryer, there is a pin
4 breaker which breaks the rigid gelatin bed of noodles
5 into large chunks which are then conveyed on to a mill
6 for grinding.

7 Next slide, please.

8 The dried gelatin is ground, employing a
9 cave mill, to a particle size ranging between two and
10 40 mesh.

11 Last slide, please.

12 Each gelatin extract is sampled and tested
13 for a broad range of physical, chemical, and
14 microbiological characteristics which are specified by
15 customers and meet the requirements of the U.S.
16 Pharmacopeia and/or through chemical codex.

17 The extracts are stored into inventory
18 prior to use in the manufacturing of final product
19 lots.

20 That concludes my presentation. Thank you
21 for your attention. Thank you for the invitation.

22 CHAIRMAN BROWN: Thank you very much, Dr.
23 Dunn.

24 Well, for me, that's quite an education.
25 I especially like the idea of wet gelatin noodles.

1 It's too bad they have to be dried before they are
2 distributed.

3 We have about 40 minutes available to us
4 before noon, which is when I propose to have our lunch
5 break, and I'm sure there will be many questions now.
6 I reserve the right to break into the discussion if it
7 becomes a little premature in the sense that this
8 afternoon we're going to have a fair amount of
9 information given to us about methods by which the
10 spongiform encephalopathy agents can be inactivated.

11 I am sure that, in the course of trying to
12 put together that information with the information we
13 have just heard, we're going to have a pretty
14 detailed, point by point analysis of what steps in the
15 processes we've just heard would or would not be
16 effective and how effective they might be, but I think
17 we can go ahead and start anyway and see where the
18 discussion goes.

19 So the Chair is open for questions. Yes?

20 MR. FAITEK: Dr. Brown, are non-bovine
21 products, gelatin or otherwise, within the purview of
22 what this committee is supposed to discuss?

23 CHAIRMAN BROWN: As we have 40 minutes,
24 why don't we see?

25 MR. FAITEK: Okay. Then the question is:

1 Apparently, porcine products haven't been mentioned in
2 any of the literature. Does that mean that porcine
3 products are not a danger for transmission of TSE?

4 CHAIRMAN BROWN: It probably doesn't mean
5 that, rigorously speaking. The pig is susceptible to
6 be -- well, to BSE -- to, in fact, yes, to BSE,
7 experimentally; that is, if you inoculate into the
8 brain or feed a pig with material -- Excuse me?

9 DR. HUESTON: Not feed. Only under
10 inoculation.

11 CHAIRMAN BROWN: Right. Well, I was going
12 to say, the feeding didn't work, but the inoculation
13 of the brain did. The point is, it is a susceptible
14 species, but to the best of our knowledge, in nature
15 no pig has ever been identified to have died from or
16 been afflicted spongiform encephalopathy.

17 Therefore, in the broad scheme of things,
18 pigs would certainly have to be considered less
19 important as a source of this disease than are cattle.
20 I'm trying to say that we cannot absolutely exclude
21 the pig from consideration, but it would certainly, on
22 the basis of what we know vis a vis the cow, be vastly
23 less important.

24 Yes, Larry?

25 DR. SCHONBERGER: On that same issue, I

1 think Dr. Dunn mentioned that vaccines in the United
2 States only contained the porcine --

3 DR. DUNN: To the best of our --

4 DR. SCHONBERGER: -- because we have a
5 document that was given to us that listed a number of
6 vaccines. It says gelatin. Many of them after
7 gelatin say pigskin only. Some leave that as a
8 question. Are you now saying that we don't have to
9 have that as a question anymore? It's all porcine?

10 DR. DUNN: To the best of my knowledge, at
11 this moment from the data we're aware of, all of the
12 customers that are making vaccines and surgical
13 sponges derive that material from porcine gelatin.

14 CHAIRMAN BROWN: Other questions. Yes,
15 Sidney?

16 DR. WOLFE: This is just a follow-up on
17 what I was raising earlier. Given that you're using
18 crushed bone in the first presentation by Dr.
19 Wrathall, what is the evidence that there isn't any or
20 there's only a minimal amount or what looking has
21 there been for neural tissue which would probably get
22 through a lot of those processes?

23 DR. WRATHALL: I think that there will be
24 a presentation this afternoon, I believe, by Dr.
25 Schrieber addressing that.

1 DR. WOLFE; Okay.

2 CHAIRMAN BROWN: Yes, again?

3 MR. FAITEK: To Dr. Wrathall, is the
4 presentation you made on the process -- Is that fairly
5 typical of the industry or is that -- were you
6 describing Eastman's process in this?

7 DR. WRATHALL: I cooperated with Dr.
8 Michael Dunn. We represent the only two manufacturers
9 in the United States that use that process, and so the
10 information that I gave was representative or across
11 the range of conditions for both of our processes.

12 MR. FAITEK: What other processes are you
13 aware of that are drastically different from the ones
14 that you described?

15 DR. WRATHALL: I'm not familiar with the
16 European process, but I would expect it to be very
17 similar to the process that I described.

18 MR. FAITEK: So this is widely used in the
19 United States, the process that you described?

20 DR. WRATHALL: Yes. As I mentioned, in
21 the United States there is only the two companies that
22 use that, and this is a summary of the conditions used
23 by both companies.

24 CHAIRMAN BROWN: Yes, Dr. Wolfe again.

25 DR. WOLFE: At the risk of offending the

1 statement that you made, Dr. Brown, since neither of
2 you, Dr. Wrathall or Dr. Dunn, are making
3 presentations this afternoon, and since when the
4 survey that FDA described was done on the question of
5 does gelatin processing result in destruction of BSE's
6 infectious agent, all of the responses were that they
7 were not doing any ongoing studies themselves, and
8 they were only aware of data provided by GMIA.

9 Could you just at least tell us the source
10 or what that data were?

11 DR. DUNN: To clarify that, that was put
12 together by both GMIA and GME in Europe, both the
13 American and European organizations, but most of the
14 data --

15 DR. WOLFE: And what are those data,
16 though?

17 DR. DUNN: Data that relate to infectivity
18 are studies that were done exclusively in Europe.

19 DR. WOLFE: And have you provided those to
20 the FDA?

21 DR. DUNN: Yes. All of that information,
22 all updated.

23 DR. WOLFE: Okay. So that's what they --
24 They're referring to the studies that were mainly done
25 in Europe on --

1 DR. DUNN: That's correct.

2 DR. WOLFE: -- the infectivity after or
3 through your process that you've described?

4 DR. DUNN: Whereas to the processing steps
5 and their effect on reducing the --

6 DR. WOLFE: And this is both the bone and
7 the pork skin or what?

8 DR. DUNN: This is only bone.

9 DR. WOLFE: Only bone? Okay.

10 DR. DUNN: Hide and bone.

11 DR. WOLFE: Okay. So FDA has that then?

12 DR. DUNN: That's correct.

13 CHAIRMAN BROWN: Dr. Asher?

14 DR. ASHER: Dr. Dunn, you mentioned that
15 the predominant source of raw material --

16 CHAIRMAN BROWN: I think you're going to
17 have to use a table microphone, Dave.

18 DR. ASHER: Doug, you mentioned that the
19 predominant source of raw material for pork skin
20 gelatin was U.S. and Canadian pigskins. Are you able
21 to share with us what the other sources are?

22 DR. DUNN: No, I don't think I said that.
23 I was just saying that the predominant source of raw
24 material for gelatin in general is from pork skin,
25 meaning that most of the gelatin in the United States

1 is pork skin gelatin.

2 DR. ASHER: But pork skin gelatin is
3 sourced only from pork skins?

4 DR. DUNN: That's right. That's correct.

5 CHAIRMAN BROWN: Dr. White, did you have
6 a question or did you --

7 DR. WHITE: The same question.

8 CHAIRMAN BROWN: Okay. Yes, Dr. Hueston?

9 DR. HUESTON: In terms of sourcing of the
10 pork skins, do pork skins and hides and bones trade
11 through brokers or do the gelatin manufacturers have
12 source contracts with the slaughter plants for their
13 direct delivery?

14 DR. DUNN: At least in the case of pork
15 skins, the latter that you stated is the case, direct
16 contracts with the slaughter plants.

17 DR. HUESTON: And how about for bones and
18 hides?

19 DR. WRATHALL: That's also true of us. We
20 have direct contracts with the major meat packing
21 companies to provide us with the bones for use in
22 gelatin manufacture.

23 DR. HUESTON: So to the best of your
24 knowledge, there would not be bones or hides or pork
25 skins being traded as a commodity by a broker where

1 they would lose the identity between the plant where
2 they were produced and the manufacturer that was
3 utilizing them. Is that --

4 DR. WRATHALL: That's to the best of my
5 knowledge, yes.

6 CHAIRMAN BROWN: I have a question also
7 for both of you, and I'm sure it will occur to
8 everybody.

9 As autoclaving is one of the more
10 effective methods for decontaminating the spongiform
11 encephalopathy agents, and as all of these processes
12 have as a goal the disruption, molecular disruption of
13 three-dimensional tissue, what happens to your product
14 if you run it through an autoclave for more than 13
15 seconds?

16 DR. WRATHALL: I think one comment that I
17 might make is that using the sterilization procedure
18 that we use does have a minimum effect, a small
19 effect, in reducing the viscosity and causing
20 additional bond breakage to occur.

21 I'm not aware of any studies looking at
22 really extensive times at those temperatures.

23 CHAIRMAN BROWN: Dr. Rohwer?

24 DR. ROHWER: Could you give us one more
25 point of clarification, which is: Are these exposures

1 at atmospheric pressure or are they under pressure?
2 Even as brief as they are, are these really flash
3 drying steps or are they true sterilizations. I
4 forget. One of them was at 258 degrees Fahrenheit, I
5 believe for 13 seconds, but is that 258 degrees under
6 pressure?

7 DR. DUNN: These are typical steam
8 injection types of treatments under these conditions.

9 DR. ROHWER: But you know that the
10 contents in the vessel actually makes an excursion to
11 258 degrees or the steam is at 258 degrees?

12 DR. DUNN: There is an enclosed loop, and
13 a temperature in there comes to that temperature.

14 DR. ROHWER: I see. So it's being passed
15 through a pipe at that temperature?

16 DR. DUNN: That's right.

17 DR. ROHWER: Okay. Thank you.

18 CHAIRMAN BROWN: Yes from the back, a
19 question?

20 DR. TABOR: You showed a list of eight
21 manufacturers that are members of your institute. To
22 what extent might there be smaller companies making
23 gelatin in addition in the United States, and if none,
24 what percentage of the market for gelatin in the
25 United States do your eight companies provide?

1 CHAIRMAN BROWN: Excuse me. Would it be
2 helpful, Dr. Freas, if speakers from the room
3 identified themselves?

4 DR. TABOR: Okay. I'm Dr. Edward Tabor
5 from the Food and Drug Administration.

6 DR. DUNN: The companies that I listed are
7 the only significant manufacturers of gelatin that I
8 know of in the United States. If there are smaller
9 companies, those are companies that I'm not aware of.

10 CHAIRMAN BROWN: Yes, Dr. Hellman?

11 DR. HELLMAN: Dr. Hellman, FDA, and this
12 is just a follow-up on a quick question that Dr.
13 Hueston had.

14 Many of the materials that are used by
15 manufacturers in products that come to us as
16 submissions are provided by suppliers, and the
17 question that I have is: To what extent do you
18 provide information to suppliers to document both the
19 sourcing of the material and its preparation?

20 DR. DUNN: Basically, the information that
21 we'll provide to our customers is similar to what I
22 showed on the slide there, stating that the materials
23 that we use to make our material are derived from USDA
24 inspected plants directly in the United States.

25 DR. HELLMAN: And for the U.S. source of

1 gelatin, how many of the supplier industry to you
2 represent? That is, you and Dr. Wrathall? I know
3 we've talked about this before, and we don't have an
4 exact handle on that.

5 This is also to follow up on a question
6 that Dr. Rohwer had about smaller manufacturers.

7 DR. DUNN: I'm not absolutely sure who
8 else is out there, but my guess is that we make up--

9 DR. HELLMAN: Ninety-eight percent?

10 DR. DUNN: Yes, something like this.

11 DR. HELLMAN: All right. Yes. We just
12 wanted to get a handle on the universe, so to speak.
13 Thank you.

14 CHAIRMAN BROWN: Dr. Roos?

15 DR. ROOS: You mentioned that the vaccine
16 gelatin is pigskin derived, and I wondered about the
17 vascular graft gelatin, as well as capsules and
18 tablets used in the United States.

19 DR. DUNN: Tablets -- that's not
20 exclusively pigskin gelatin. That's going to be a mix
21 of bone and pigskin gelatin. The grafts -- I'm not
22 sure. I can't answer that. I don't have that
23 information.

24 CHAIRMAN BROWN: A question from the
25 floor.

1 DR. RICHMAN: I am Paul Richman. I'm with
2 the Office of Vaccines.

3 I just wanted to make a clarifying comment
4 about the gelatin that's used in vaccines. The
5 information we have at this point indicates that a
6 large percentage of it is porcine gelatin, but there
7 are some vaccines that do use bovine gelatin.

8 CHAIRMAN BROWN: From the industry's point
9 of view, why do you -- Are there different uses -- I
10 mean, you showed different uses for pigskin gelatin
11 versus bone gelatin. Just speaking commercially, why?
12 I mean, what is -- Is it different purities, a
13 different grade, different viscosity?

14 What determines whether you use pig's
15 skins or cattle's bones for a gelatin product or are
16 they completely interchangeable, and it's just a
17 matter of what's available?

18 DR. WRATHALL: I could comment that, in
19 the case of the limed ossein gelatin, this is
20 predominantly used for photographic purposes, due to
21 its certain coating characteristics and also it tends
22 to have a lower photographic activity.

23 CHAIRMAN BROWN: So most of the limed
24 gelatin goes -- that in this country, as far as you're
25 aware, most of the limed gelatin -- that is to say,

1 ossein -- is destined for photographic purposes?

2 DR. WRATHALL: I believe a major part of
3 it would go into photographic purposes, yes.

4 DR. WOLFE: And where does the rest go in
5 for then, the stuff that doesn't go for photographic
6 purposes?

7 DR. DUNN: It would go to pharmaceutical,
8 and a very small amount to edible. So it's really
9 split between photo and pharmaceutical. You get on
10 the pig side, and it's primarily food. It's primarily
11 food and pharmaceutical; but the requirements are much
12 more stringent on the pharmaceutical and photographic
13 side, both microbiologically and chemically.

14 CHAIRMAN BROWN: That is, pharmacologic
15 and photographic are more stringent than food?

16 DR. DUNN: Well, the only thing I can
17 think of is ash. There's not a stringent ash
18 requirement so much on the food side as there is on
19 both the photo and pharmaceutical side. So we're not
20 cutting any corners there in terms of microbiological
21 characteristics.

22 CHAIRMAN BROWN: Dr. Hsiao?

23 DR. HSIAO: Dr. Wrathall, when you had one
24 of your slides, you said there was Type A and Type B,
25 and under Type B there was the ossein limed, and then

1 there was another one which was called bovine hide
2 alkali processing, and we haven't heard anything about
3 bovine hide alkali processing. Could you comment on
4 how that's done?

5 DR. WRATHALL: I'm not very knowledgeable
6 on that process. I do understand, though, that it
7 goes through an alkali caustic pretreatment similar to
8 the lime process and is exposed to high pH, perhaps
9 even higher pH than the bone process.

10 DR. HSIAO: But is it exposed for whatever
11 -- let's see -- 35-70 days?

12 MR. WISEMAN: Excuse me. I'm Gerry
13 Wiseman.

14 The limed alkali pretreated hide have the
15 identical process to the ossein process. The only
16 thing in the bone is bone has a pretreatment to remove
17 the minerals so that it can be extracted, but once you
18 get to that point they're identical processes. High
19 alkali content, a long time.

20 DR. HSIAO: But for the same duration?

21 MR. WISEMAN: Yes.

22 DR. WHITE: And in the same processing
23 plants? I mean, are bovine and porcine done in the
24 same place?

25 MR. WISEMAN: Yes. They can be.

1 DR. HSIAO: So that means that following
2 acidulation, -- there's the degreasing and acidulation
3 which are for the bone. Then everything else after
4 that pertains to the hide as well?

5 MR. WISEMAN: Yes.

6 CHAIRMAN BROWN: Is there any reason --
7 Again to come back to this distribution between skin
8 and bone, is there any reason why the bone sourced
9 gelatin is not characteristically used in foodstuffs?

10 MR. WISEMAN: Part of it is economics,
11 really. The bone is a more expensive source, has a
12 lot more pretreatment, whereas pig skins or, you know,
13 or cattle hide can be used directly without that
14 pretreatment. So a lot of it is economics and
15 availability.

16 CHAIRMAN BROWN: Can you give me an idea
17 of what proportion of global -- of the global usage of
18 gelatin comes from the pig skin process versus the
19 bone process? I mean, I infer from what you say that
20 most of it goes to foodstuffs, because you introduced
21 the concept of economics.

22 MR. WISEMAN: Well, Dr. Schrieber has
23 slides on that, but prior to that, in essence, in the
24 United States about 55 percent of the gelatin produced
25 is from a pig skin source, and perhaps in the

1 twenties, low twenties, from hide and from bone.

2 So there's a --

3 CHAIRMAN BROWN: So about half of the
4 gelatin produced in this country goes toward food
5 products?

6 MR. WISEMAN: Probably a bit more than
7 that.

8 CHAIRMAN BROWN: Two-thirds?

9 MR. WISEMAN: We don't have -- It's very
10 difficult for us as an industry to accumulate all of
11 that data, because we're individual manufacturers, and
12 we don't share customer data and where the gelatin is
13 going to; but good judgment would say that about two-
14 thirds of the gelatin is going towards food.

15 CHAIRMAN BROWN: Dr. Hsiao.

16 DR. HSIAO: Is there any particular reason
17 why there's a difference in the -- why bovine hides
18 are treated with alkali, which takes like days -- it
19 takes like 100 days or something like that -- whereas,
20 pig hides are treated with acid, which only takes two
21 to four days? Is it just for historical reasons?

22 MR. WISEMAN: It has to do, really, with
23 how strongly the collagen is bonded, and just as a
24 rule of thumb, the younger the animal is, the less
25 bonding there would be for collagen to collagen bonds

1 that have to be broken.

2 So if you looked at progression of chicken
3 to a hog to cattle to an elephant, you would find that
4 the age of the animal has a great deal -- and cattle
5 are older animals, much more structured collagen,
6 takes stronger chemical treatment to break those
7 bonds, and so it's a longer process than the pig skin
8 process.

9 CHAIRMAN BROWN: Ms. Harrell.

10 MS. HARRELL: Mr. Chairperson, I hope it
11 is appropriate at this time -- and I didn't understand
12 exactly what you said about this afternoon's session,
13 but my basic question would be: These processes that
14 have been described here, are they proven to
15 inactivate the BSE agent and other TSE agents?

16 CHAIRMAN BROWN: I think that Dr.
17 Schrieber will have a good deal to say about that this
18 afternoon, but I can give you a little preview, that
19 the answer will be no.

20 Question from the floor?

21 MS. FANG: Florence Fang from FDA. One of
22 the events that led to the current BSE epidemic is
23 attributed to the elimination of the hydrocarbon
24 solvent extraction system processing in the rendering
25 process.

1 Now if we can forget about EPA for the
2 time being, is it practical to introduce a solvent
3 extraction step in the manufacture of gelatin? It
4 helps to degrease.

5 MR. WISEMAN: Well, first of all, the
6 solvents in gelatin, once you've extracted gelatin,
7 most solvent will create -- will insolubilize gelatin.
8 They will precipitate and would affect the physical
9 properties.

10 So while anything is possible, I don't
11 think we know how to do that. We've never solvent
12 extracted, to my knowledge. Gelatin does not dissolve
13 in solvents.

14 MS. FANG: I would imagine, you know, the
15 introduction of the solvent extraction will be prior
16 to the liming or the process at just the bone -- at
17 the bone stage, not after the hydrolysis.

18 Of course, you know, even the
19 effectiveness of such a step will still have to be
20 determined.

21 MR. WISEMAN; In the rendering process
22 solvents were used in Europe, particularly in the
23 U.K., to remove fat from bone and flesh material.
24 From a gelatin standpoint, it's something that -- I
25 mean, I couldn't comment on whether it would be

1 effective or not. I have absolutely no idea of that.

2 It would be very difficult, and you would
3 certainly have food problems removing the solvent once
4 you've added it. I mean --

5 MS. FANG: Yes, sure. I mean, I would
6 imagine, if it is introduced, it will be at the very
7 beginning.

8 CHAIRMAN BROWN: Dr. Rohwer has something
9 to add to that.

10 DR. ROHWER: I'd like to make a comment
11 about that question. First, David Taylor at the
12 Neuropathogenesis here in Edinburgh has looked at the
13 earlier rendering process and saw that extraction and
14 has some data which suggests that quite likely the
15 earlier rendering methods were incapable of completely
16 inactivating these agents as well.

17 So perhaps, although extraction itself is
18 not the solution, I think the point of the question
19 was could the industry consider adding specific steps
20 for viral removal to make these products safer. That,
21 it seems to me, is a valid consideration, and there
22 are actually a wide number of possibilities that could
23 be looked at, and some of the, hopefully, would be
24 compatible with product integrity.

25 CHAIRMAN BROWN: Dr. Honstead, did you --

1 DR. HONSTEAD: John Honstead from FDA.
2 Our understanding was that it wasn't the solvents in
3 solvent extraction rendering that was accomplishing
4 the inactivation. It was the steam used to remove the
5 solvents from the final product that possibly was
6 inactivating the TSE agent.

7 CHAIRMAN BROWN: I think that perhaps Dr.
8 Rohwer would say something or needs to, but I think
9 probably it's a combination of both. Solvents, in and
10 of themselves, do have an inactivating effect which is
11 not complete, but it's still not bad.

12 Steam, by itself, has an inactivating
13 effect under the proper conditions, and when the two
14 of them are combined, I don't know the effect is
15 additive, but the likelihood is that solvent
16 extraction under steam is more effective than either
17 steam alone or hydrocarbon solvents alone.

18 Yes, sir?

19 MR. BAILEY: John Bailey with Food and
20 Drug. I have a quick couple of questions about the
21 manufacturing process and some possible variations on
22 it.

23 Given the large volumes of acid and base
24 that are likely to be used, are any of these recycled
25 in the process and reused, given, say, the different

1 processes that different companies use, or maybe more
2 appropriately, is it possible that some -- could
3 reagents be recycled and reused in the process?

4 DR. WRATHALL: As far as I know, in the
5 limed ossein process the lime is not recycled for use
6 in the process. It's a one-time use only.

7 DR. DUNN: That's true for pork skin as
8 well, too. It's acidified. I guess that pH is one to
9 three, and that's just -- It's washed out with water
10 and is not recycled.

11 CHAIRMAN BROWN: As you were describing
12 the process -- and I know the question about the EPA
13 came up -- I was wondering if any of these input
14 animals were infected, you have probably in the
15 course of a year thousands and hundreds of thousands
16 of gallons of effluent and, if it isn't in the
17 finished product or gelatin, it would certainly be in
18 the effluent.

19 There's a question that sometimes is never
20 raised, is what's not there as opposed to what's
21 there, and that's not the focus of today's discussion;
22 but the washing steps are so enormous in the process
23 of gelatin that any input infectivity would certainly
24 have to be out the wash, so to speak, if it wasn't in
25 the final product.

1 Yes, Dr. Roos?

2 DR. ROOS: I wondered whether any of the
3 sourcing or processing has changed since the BSE was
4 identified or is the way things were pretty much done
5 15 years ago?

6 Second, are there regulations with respect
7 to the processing itself or is this just a self-
8 regulated manufacturing aspect? We're given gelatin
9 in a final product, and how it's made is how the
10 manufacturer essentially chooses to make it.

11 DR. WRATHALL: I don't know for a fact
12 what the sourcing has been. I would expect it has
13 been very similar to what -- in the past to what we
14 have shown in our presentations.

15 DR. DUNN: But in the terms you're talking
16 about, how we process, whether that's changed
17 significantly with this news of BSE. As far as I know
18 within the industry, the process of making pork skin
19 and bone has been the same for many years, and we
20 haven't really made any significant changes in how we
21 process things.

22 DR. ROOS: And everything is self-
23 regulated?

24 DR. DUNN: I think that's a fairly fair
25 characterization. Yes.

1 DR. ROOS: One last question: Cosmetics
2 -- is that pig skin or bovine derived product?

3 DR. DUNN: That's probably a mix of the
4 two.

5 CHAIRMAN BROWN: Since the notion of
6 source has been reintroduced, sometime in the course
7 of this meeting it might be useful in open session --
8 or perhaps not; you can decide -- to evaluate our
9 government's designation of a BSE-free versus a BSE
10 country, because it continues to be pointed out in
11 meetings by the people in these countries -- and I'm
12 thinking even of Switzerland which has about 250
13 cattle that have died from BSE, some of which are said
14 to have been born -- well, were born after all
15 precautions were taken to ensure that their disease
16 was not the result of being fed bonemeal, but these
17 nagging doubts continue to come up.

18 For example, the Swiss epidemiologist said
19 you really couldn't be sure, for example, that a cow
20 hadn't broken through a fence and started munching on
21 pig feed, and the lesson there suggests that no one
22 has yet been able to prove beyond a question of a
23 doubt that any BSE in any country other than the
24 United Kingdom has not been the result of having been
25 exposed to contaminated food.

1 So the notion of a BSE country versus a
2 non-BSE country, since sourcing is important, really
3 ought to be scrutinized, I think. I think it's
4 unlikely that you could be worried about BSE in France
5 with 23 cattle or Portugal with 20 or 30.

6 IN time we may discover that BSE has the
7 capacity to become an endemic infection, but I think
8 today we cannot say with certainty that any country
9 other than the United Kingdom has any indigenous BSE.

10 So that might be worth arguing about.

11 Larry?

12 DR. SCHONBERGER: To follow up on your point,
13 you know, certainly, at CDC we're very cognizant of
14 the fact that -- You know, how good the surveillance
15 system is can often determine the number of cases that
16 you get reported, and an element of an evaluation of
17 a country's surveillance system should be instituted
18 as part of the assessment that you're just referring
19 to in terms of determining which country is BSE or
20 which is not.

21 I think it's my understanding that the
22 Department of Agriculture is actually in the process
23 of doing just that.

24 CHAIRMAN BROWN: We'll have one last
25 comment from Dr. Faitek, and then we'll break for

1 lunch.

2 Before we do, Dr. Faitek, I think we will
3 break now or in a couple of minutes, and I would hope
4 we could reconvene at one o'clock rather than 1:15 and
5 just continue to steam ahead. Dr. Faitek.

6 MR. FAITEK: The doctor is an honorary
7 title, I just assume.

8 CHAIRMAN BROWN: Well, whatever, as they
9 say.

10 MR. FAITEK: Okay. Again, to find out
11 what the uses of these various gelatins are, I gather
12 that about 60 percent of the gelatin products that are
13 used in this country come from porcine sources. Is
14 that correct?

15 DR. DUNN: That's a pretty good number.
16 I'd say between 60 and 70 is a pretty good number.

17 MR. FAITEK: Okay. And of the remaining,
18 say, 35 percent, what portion of that is used in
19 photographic products, and then the remainder would,
20 obviously, be for food products.

21 MR. DUNN: Like I said, I don't have those
22 numbers right in front of me, but I think it's more
23 pharmaceutical than photo.

24 MR. WISEMAN: That's a difficult question.
25 The industry does not share information across

1 markets, who sells who what. So we generally know the
2 total volume that's produced and where it goes to from
3 a customer standpoint, but we can only speculate.

4 This is speculation on my part, but that
5 less than 20 million pounds or perhaps, oh, 15-20
6 percent might go into the photographic side.

7 MR. FAITEK: Fifteen to 20 percent of
8 total gelatin use?

9 MR. WISEMAN: Yes. Somewhere. That's my
10 own speculation.

11 MR. FAITEK: So that would leave 15-20
12 percent going for foodstuffs or pharmaceutical.

13 MR. WISEMAN: Yes. That's probably pretty
14 accurate.

15 CHAIRMAN BROWN: That concludes the
16 morning session. We'll reconvene at one o'clock, at
17 which time we will begin with --

18 DR. FREAS: If I could make a quick little
19 announcement -- We have asked that the restaurant down
20 below reserve about 20 seats for the Advisory
21 Committee. We ask the Advisory Committee to sit in
22 those seats, because in theory the service will be a
23 little bit faster, and we'd like to see you back on
24 time.

25 Thank you.

1 CHAIRMAN BROWN: We have reserved seats.
2 (Whereupon, the foregoing matter went off
3 the record at 11:53 p.m.)

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1 ideas, as appropriate, on realistic and practical
2 approaches to maintaining surveillance for scrapie,
3 BSE, chronic wasting disease in sheep, goats, cattle
4 and deer and other domestic animals.

5 So if anyone is -- and there are a number
6 of people at this conference who actually are already
7 signed up for this electronic conference, but if there
8 is anyone else who is particularly interested, if you
9 could just write your name and either your FAX or E-
10 mail address on a piece of paper outside or see me
11 directly, and I'll make sure you get all the
12 information on how to log into the system.

13 Thank you.

14 CHAIRMAN BROWN: Thank you very much.

15 Doctors Hueston and Detwiler have a
16 comment or two to make about classification of BSE
17 countries.

18 DR. DETWILER: Thank you, sir. I just
19 want to clarify at least the USDA's classification for
20 countries that are known to have BSE. That solely
21 right now is we recognize countries where BSE is known
22 to occur, and that's based on the country's
23 surveillance and reporting system, if they have
24 reported BSE in native animals. Then they are --
25 regulation -- The interim rule is placed in the

1 Federal Register and they are added as part of the
2 Code of Federal Regulations, Title 9.

3 We do not maintain a separate list of
4 countries that are considered BSE-free. It's just
5 considered all other countries other than those that
6 report BSE.

7 Dr. Schonberger had said we are probably
8 considering moving towards classifying countries as
9 risk based, and the Office of International Epizootics
10 -- they have some recommendations coming up for vote
11 in May that would look at countries and give some
12 criteria where countries would have surveillance
13 criteria risks as far as importations, etcetera.

14 So we will probably either use that
15 criteria or implement some others.

16 DR. HUESTON: I just was going to
17 reiterate that there is no international standard for
18 the characterization of countries as being free of BSE
19 or, for that matter, free of any of the other
20 transmissible spongiform encephalopathies, that the
21 International Office of Epizootics -- There, the
22 proposals that are coming forth now are, as Linda
23 says, risk based, and they will also have specific
24 requirements on numbers of cattle brains which must be
25 examined in order for a country to establish or

1 suggest that they are free of these diseases or that
2 those diseases do not exist.

3 CHAIRMAN BROWN: Thank you very much.
4 That really does introduce us to the afternoon's first
5 topic, which has to do with risk, exposure estimates
6 and risk assessment.

7 I would like to say here that we all
8 understand, I think, without exception that the risks
9 that we are considering today are very, very small,
10 but they may not be zero. So it, to exaggerate, is
11 really talking about whether the risk is tantamount to
12 someone jaywalking across a busy intersection, on the
13 one hand, or someone drowning in Glasgow because there
14 has been a volcanic eruption in Iceland, on the other.

15 One is so small as to negligible. The
16 other is small but not negligible, and somewhere
17 between these two extremes is where we are positioned
18 today. We are not talking about the risk of getting
19 BSE in people who are habitual eaters of cow brains.

20 This is not the issue that we are talking
21 about, just so when we are in the midst of deep
22 discussions about risk and risk assessment, we know
23 that we are always at the low end of the scale. The
24 question is just how low.

25 With that introduction, I will ask Dr.

1 DiNovi to initiate the exposure estimates and risk
2 assessment part of this forum. Dr. DiNovi.

3 DR. DiNOVI: Well, much of my background
4 will seem familiar, as it was gone over mostly this
5 morning already.

6 My name is Michael DiNovi. I am with the
7 Office of Pre-market Approval at CFSAN, and one of my
8 jobs is to estimate exposure to ingredients in the
9 diet, for which gelatin certainly qualifies.

10 Next slide, please.

11 Well, as you've seen and heard, gelatin is
12 ubiquitous, and between food, pharmaceuticals and
13 cosmetics, we assume that everyone is exposed to
14 gelatin in one form or another.

15 Next slide, please.

16 Use in food typically ranges from about a
17 tenth of a percent to two and a half percent of
18 finished product. You've seen the types of foods that
19 it occurs in, like gelatin desserts, meats, candies,
20 so on.

21 In the first five bullets I have here,
22 gelatin would appear as an ingredient on the label.
23 There are some foods containing microencapsulated
24 ingredients, flavors or sweeteners perhaps, where the
25 gelatin would not be labeled. So that's one of the

1 few cases where you would not know you were consuming
2 a food that contained gelatin.

3 Next slide.

4 Pharmaceutical uses you've seen before,
5 variable levels depending on the particular
6 application.

7 Next, please. Also cosmetic uses are
8 variable.

9 As I said earlier and, as you've heard,
10 everyone is exposed to gelatin in one form or another
11 during their lifetime.

12 Next slide.

13 This gives us some actual numbers. Last
14 year as part of the GRAS information for gelatin, we
15 estimated exposure to gelatin from its use in food.
16 For a typical food ingredient exposure, you combine
17 use levels in a food with a food intake to come up
18 with an exposure.

19 We used USDA data -- that is to say, food
20 intake data and ingredient levels, and we arrived at
21 a 700 mg per person per day exposure for someone
22 consuming at the mean level, and about a gram and a
23 half for someone consuming at the 90th percentile
24 level. This is food, all gelatin, all sources.

25 Next slide, please.

1 In this case today, we are more interested
2 in total exposure from all of the various routes. In
3 order to do that, we do not have the kind of data we
4 would use specifically for foods. So we would take
5 into account that everyone is exposed and simply use
6 the total poundage of gelatin disappearing into the,
7 in this case, consumer product stream to come up with
8 an exposure.

9 Now as I mention here, exposure from
10 cosmetic use on healthy skin should be minimal, and is
11 probably ignorable. However, where there's skin
12 damage, it's possible that there would be some
13 transport of gelatin.

14 Now this -- My bullet here on bovine
15 gelatin -- That refers to the total amount of gelatin,
16 both domestically produced and imported, that's used
17 in the United States. Forty-five percent is from --
18 Well, to be fair, 55 percent is from pork.
19 Conservatively, assuming that the rest of it is
20 bovine, 45 percent is bovine.

21 In 1995, 60 million pounds total gelatin
22 disappeared, which works out to a per capita exposure
23 of approximately 300 mg per person per day or, if you
24 just consider bovine, 130 mg per person per day.

25 Next slide.

1 The final issue I would touch on today is
2 the ratio of imported to domestically produced
3 gelatin. In 1995 we have data that suggests that
4 about 40-45 percent of total gelatin being used in the
5 United States is imported.

6 From BSE countries, as listed there,
7 3,000-4,000 metric tons is imported. Now if you just
8 -- With that exposure separate here, if you just
9 consider those 3,000-4,000 metric tons, your exposure
10 per capita would be about 100 mg per person per day
11 or, to look at a high, 90th percentile, take 200.

12 Finally, just to emphasize stuff that
13 you've heard before, no bovine gelatin is prepared
14 from herds in the U.K. It's all imported and
15 prepared, and there are very few French herds that are
16 affected. The vast majority of that 3,000-4,000
17 metric tons is from France and England.

18 Thank you.

19 CHAIRMAN BROWN: Are there any questions
20 for this presentation from either the floor or the
21 committee members?

22 I was a little confused about the first
23 slide which said that 0.3 to about 1 gram a day of
24 gelatin is consumed in foods, and then another slide,
25 you had -- or I had read that the figure was just 0.3.

1 Those figures went by fairly quickly.

2 DR. DiNOVI: Why is the number higher just
3 for food?

4 CHAIRMAN BROWN: I'm sorry?

5 DR. DiNOVI: You're wondering why is the
6 number higher just for food?

7 CHAIRMAN BROWN: Well, I guess I'm
8 wondering -- Yes. I missed a beat somewhere along the
9 line.

10 DR. DiNOVI: Okay. The first data that I
11 spoke of were just the levels of gelatin in food
12 multiplied by those foods' intakes. So what you're
13 looking at are short term food intake surveys where
14 not everyone eats all of the foods that contained
15 gelatin during the survey period. That's a maximizing
16 assumption.

17 What we would say, and what we did say,
18 for example, in this GRAS affirmation -- and GRAS, by
19 the way, Generally Recognized As Safe -- is that this
20 is a conservative exposure. In this specific case
21 today where we're dealing with numerous sources, food,
22 drugs and cosmetics and what-not, implantables, the
23 best way to get a handle on a real number is to use
24 the total amount of gelatin that we know is
25 disappearing into consumer products.

1 So there's two different bases that these
2 numbers are derived from. So the per capita number
3 will necessarily be lower.

4 CHAIRMAN BROWN: So the per capita average
5 intake, based on gelatin disappearing, is about a
6 third of a gram a day?

7 DR. DiNOVI: Right.

8 CHAIRMAN BROWN: Of which approximately a
9 half comes from cows -- that's a bovine origin -- of
10 which a very small proportion comes from BSE positive
11 -- so called positive countries. Is that the bottom
12 line?

13 DR. DiNOVI: Yes.

14 CHAIRMAN BROWN: Okay. I'm sorry.
15 Question? Yes?

16 DR. HOEL: Again on these numbers, when
17 you did your total math to get your .3 grams, that's
18 imported and locally produced gelatin. What about
19 products that are imported that contain gelatin?

20 DR. DiNOVI: That is not -- That is a good
21 point. That is not considered here. This is gelatin
22 itself disappearing, not products that are made with
23 gelatin and then imported.

24 DR. HOEL: So that could bring some of the
25 number up. The difference between the .7 and the .3.

1 DR. DiNOVI: Yes. It would bring it up
2 somewhat. Yes.

3 DR. HOEL: Second question: On the
4 imported -- 45 percent imported, how much of that is
5 from EU countries or does it come from all over the
6 world?

7 DR. DiNOVI: Well, some from South America
8 and some from -- more from South America than Europe
9 is my understanding. 3,000-4,000 metric tons, as I
10 said here, is just from the BSE countries, from
11 France, England -- mostly from France and England,
12 actually. There's also Germany. I'm not exactly sure
13 where it's all coming from. South America and Europe,
14 certainly.

15 DR. HOEL: Okay.

16 CHAIRMAN BROWN: So that there really are
17 three avenues for exposure to gelatin. One would be
18 gelatin sourced in this country, manufactured in this
19 country and sold in this country. A second would be
20 gelatin imported from another country, manufactured
21 into products in this country. The third would be
22 products imported from other countries that contain
23 gelatin manufactured there.

24 DR. DiNOVI: Yes, that's correct.

25 DR. HUESTON: And would there not be a

1 fourth, and that would be where raw material comes
2 into the U.S. and is manufactured, just to complete
3 the list?

4 DR. DiNOVI: It's my understanding that
5 that's not an occurrence. You mean like hide splits
6 and bone? Is that what you mean when you say material
7 imported?

8 DR. HUESTON: I thought we just heard that
9 some -- Are there not some bones coming into the U.S.?

10 DR. WRATHALL: Approximately two percent
11 of the bones come from Argentina for use in the United
12 States in gelatin manufacturing.

13 DR. HUESTON: Right, and --

14 DR. WRATHALL: And the rest is from the
15 United States.

16 DR. HUESTON: And there are hides coming
17 into the U.S., hide trimmings that are coming into the
18 United States.

19 CHAIRMAN BROWN: So I have this image in
20 my mind of a huge cargo ship filled with cattle bones
21 coming up from Argentina from time to time. Is that
22 like banana boats?

23 DR. WRATHALL: They do come up in
24 containers, yes.

25 CHAIRMAN BROWN: Dr. Bolger.

1 DR. BOLGER: Hi. I'm Mike Bolger. I am
2 a toxicologists, and I'm the head of the Contaminants
3 Branch in the Center for Foods.

4 What I was asked to do today was to
5 provide a brief overview of how we approach safety
6 risk assessment, particularly in foods, but I think it
7 also is an apt description of the same approach that's
8 taken by the other centers, with the possible
9 exception of the pharmaceutical approach where you
10 have the efficacy consideration, which is a major one,
11 taken into account.

12 I'm not here to present you a risk
13 assessment on BSE in gelatin. I want to make that
14 very clear. What I'm trying to do is to describe the
15 safety risk assessment framework in which we operate
16 and to articulate and identify what I see as some of
17 the major issues that are going to have to be dealt
18 with in any kind of safety risk assessment
19 consideration.

20 What you see in the first slide -- and
21 like any risk assessor worth their salt, I have to
22 start off with a risk assessment paradigm. This
23 paradigm is a variation of a theme that was first
24 described by the National Academy of Sciences in 1983,
25 and most recently operated, if you want to put it that

1 way, in 1995.

2 What we attempt to do in this risk
3 assessment paradigm is to sort of lay out the
4 different steps in the process. Obviously, in any
5 kind of public health consideration, the ultimate and
6 really the first question that is really asked,
7 particularly by the public, is they want to know is it
8 safe, whether we're talking about BSE or Dobsons or
9 methyl mercury or food additives or whatever.

10 Generally, the answer that comes back is
11 some statement of whether this exposure is safe or not
12 safe, but for some issues like BSE this question may
13 not be sufficient, and we then have to move to the
14 next tier in the risk assessment paradigm where we
15 talk about risk.

16 I'm going to make a distinction about what
17 I call a safety assessment and risk quantitative risk
18 assessment, because I think they are somewhat just all
19 part of what we call risk assessment. Many times --
20 and I find myself in these kinds of discussions --
21 there's a very different concept on the part of
22 discussants on what risk assessment really is, and you
23 find out many times that when you're talking with
24 someone, their concept of risk assessment is what I
25 would call safety assessment, which is different in my

1 mind in terms of what we call quantitative risk
2 assessment, which then gets into some very good key
3 issues like adversity and some very significant issues
4 of variability of the adverse response and the issue
5 of uncertainty.

6 How do we deal with uncertainty? Of
7 course, uncertainty is a major problem here in this
8 BSE issue.

9 I just wanted to briefly identify under
10 the Food, Drug and Cosmetic Act, which is the
11 statutory authority under which we operate, there are
12 some rather specific risk standards that are
13 identified in the statute that deal with contaminants.

14 Under one particular section called
15 403(a)(31), there are really two risk standards that
16 Congress identified. These are not quantitatively
17 described. These are qualitatively described, but the
18 Act does make a difference between those substances
19 that are added versus those that are not added in
20 terms of the probability of harm.

21 In other words, if it's added, there is a
22 difference in terms of degree of probability that one
23 has to take into account versus something that occurs
24 ordinarily rendered where there is no apparent hand of
25 man involved.

1 Another risk standard that also applies
2 here is the risk standard identified for dietary
3 supplements, which is described as presents a
4 significant or unreasonable risk of illness or injury.
5 This at this time would appear to be something akin to
6 what we would call ordinarily rendered, which is the
7 standard we apply to naturally occurring substances.

8 Now in the basic safety assessment
9 paradigm, we basically end up identifying what we call
10 a no observed adverse effect level. This would be
11 either in an animal or a human study. The key word
12 here is observed, because we are saying -- we are
13 defining the adverse effect level as the observed
14 level, and that's a very key factor, because,
15 obviously, how hard we look and what we're looking
16 with is a major factor in how we identify this level.

17 Then we use what we call safety
18 uncertainty factors to extrapolate either from the
19 animal study using a tenfold uncertainty factor. We
20 use an additional tenfold uncertainty factor to
21 account for dose duration, differences between the
22 animal and possibly the human exposure scenario.

23 We also -- To account for intrahuman
24 sensitivity, we use an additional tenfold uncertainty
25 factor. So we end up with a cumulative safety

1 uncertainty factor of anywhere from 100 to 1,000-fold.

2 Now this is the process that's generally
3 followed for noncarcinogenic substances, using the
4 safety factor uncertainty factor approach, where we
5 are trying to describe the level that we deem to be
6 safe or acceptable. Another term that's often used is
7 the margin of safety approach.

8 Now for carcinogenic substances, just to
9 make a distinction here, we generally follow a
10 somewhat different paradigm where we use an upper
11 bound estimate of relative risk derived either from an
12 animal bioassay or from a human epidemiology study
13 where we're extrapolating downward from the observable
14 range to the range of exposures which humans are
15 realizing.

16 There has been some movement to bring
17 these two paradigms in a more common footing where
18 there's been some argument in use by approaches in
19 other countries where a margin of safety or
20 uncertainty safety factor approach is being argued to
21 be used for carcinogenic substances.

22 I think we really have to again clearly
23 identify in the beginning of the consideration what is
24 the public health question that we're trying to
25 address here. Is it a question of safety -- and when

1 I mean safety, essentially what we're trying to
2 describe is essentially a negligible or zero risk
3 level of exposure -- or is it a question of the
4 probability of an adverse effect?

5 A safety assessment does not describe in
6 any way, shape or form the probability of the adverse
7 event that you're concerned about. Should the --
8 Another major consideration that has to be taken into
9 account is should the public health question be narrow
10 in scope? In other words, should we just be looking
11 at the risk for the particular contaminant in a
12 particular food or do we have to be thinking about it
13 in a broader context of how this is an added risk
14 consideration in terms of a background risk?

15 It's important to keep in mind that the
16 safety assessment is basically a first step in an
17 iterative process, as I showed you in that paradigm.
18 It is a simple, very straightforward question. Yes or
19 no, is there some level of exposure that is safe? And
20 it's very useful for screening out trivial public
21 health problems, but it does not provide or does not
22 describe a problem, something like BSE, in a
23 quantitative fashion nor does it provide a basis for
24 gauging the level of effort by which you either
25 remediate a particular source that you're concerned

1 about for describing some public health advisory that
2 one would want to translate to the public or in terms
3 of setting a particular regulatory standard.

4 Another important factor to keep in mind
5 in terms of the safety assessment paradigm is safety
6 -- excuse me, uncertainty is managed; it is not
7 described. It is used to describe an adequate margin
8 of safety.

9 Another important point that decides the
10 safety factor is determined in large part by what we
11 do not know, not by what we know.

12 Another important point to keep in mind is
13 that this safety assessment paradigm basically ignores
14 the dose response relationship. You're basically just
15 taking a single dose level from a single study to
16 identify an acceptable level of exposure, and it
17 essentially boils down to the fact that it is a risk
18 management tool.

19 So if the safety assessment paradigm is
20 not sufficient in a consideration like BSE, then in
21 terms of quantitative risk assessment what are the
22 issues that we have to be mindful of when going to
23 that consideration?

24 First of all, we have to take into account
25 the very significant issue of dose response. What is

1 the magnitude of individual response as one moves up
2 or down the dose response curve?

3 We have to be able to describe variability
4 of response within a population. We have to be able
5 to describe uncertainty and, hopefully, in a
6 quantitative way, not just qualitatively. We have to
7 provide a descriptive analysis of this data to a
8 decision maker, so that one can gauge the level of
9 effort in terms of what is the ultimate decision one
10 reaches.

11 Another important, I think, issue in
12 talking about quantitative risk assessment is that, if
13 we're talking about competing dietary risks -- this
14 was brought up by the Chairman very briefly in the
15 beginning of this session, although I think the issue
16 of competing risk is a very -- can be one that can be
17 somewhat problematic, if you try to put it in that
18 context. I think it may be more useful to put it in
19 terms of the context of competing dietary risk.

20 I think comparing a risk from a
21 contaminant in food to being struck by lightning --
22 I'm not sure how that comparison could be made, and I
23 think it's a very difficult concept also to convey in
24 a risk communication framework.

25 What are the major uncertainties that one

1 is going to have to grapple with? Dr. DiNovi already
2 briefly outlined some of this in terms of the exposure
3 assessment, but there's variability of consumption,
4 variability of concentration and uncertainty
5 associated with these factors.

6 There's the dose response, which I've
7 already identified. There's the issue of biomarker.
8 I we're using the ingested dose as the dosimetric use,
9 that would be probably an appropriate dosimetric to be
10 used when dealing with a risk assessment, or is there
11 some other more suitable biomarker of exposure or
12 adverse effect that we should be considering?

13 The other major issue is the outcome
14 measurements in terms of interpretability. How do we
15 translate an observation in terms of its significance
16 in terms of public health? I've already alluded to
17 the background risk issue, is that there are dose
18 independent factors that have to be taken into account
19 in terms of the adverse effect that you're grappling
20 with.

21 I've already gone over some of this. So
22 I'll briefly go through this in terms of the
23 variability issues. A lot of times, the variability
24 uncertainty issues really have to do with the context
25 of what you're looking at, but there's the differences

1 in dietary concentration, differences in types and
2 rates of food consumed, and there's underlying
3 physiological differences. There's age differences.
4 There's sex differences, weight differences, and many
5 other underlying physiological issues.

6 In terms of uncertainty, there are errors
7 associated with data collection. There's sampling
8 error. There's measurement error. There's also the
9 uncertainty associated with -- particularly, if you're
10 in a modeling exercise, which is a very useful step in
11 terms of risk assessment -- is the uncertainty
12 associated with the modeling paradigms that you're
13 using. Then there's the issue of multiple datasets.
14 How do you merge or converge different datasets, or
15 can you do it and, if you do that, how do you treat
16 them? Do you weight them in some fashion?

17 Now specifically in regards to the BSE
18 issue, some of this, obviously, is redundant, and
19 you're very familiar with it. That is, this is a new
20 animal -- BSE is a new animal disease identified in
21 1986. The peak appears to have occurred in 1992.

22 Variant CJD may be related to BSE. This
23 is a major uncertainty that one is going to have to
24 deal with. It's also important that beef consumption
25 was, and is, widespread and variable in the U.K.

1 I think that one of the major problems
2 here is that uncertainty in terms of risk assessment
3 of BSE and variant CJD is extremely large. There's
4 the inability to test for human disease. The
5 incubation periods with human disease may vary from
6 ten to 25 years. It's a anybody's guess, and you
7 could list -- You come up with a rather lengthy list.

8 The expected frequency of variant CJD in
9 the U.K. is highly uncertain. That's the only
10 conclusion that one can draw, and that's obviously
11 from the study that was published recently by Cousens
12 and co-workers, which I think you have in your
13 package.

14 This is a graphical summary presentation
15 of the predicted numbers of variant CJD from the
16 Cousens, et al. study. Along the X axis you have what
17 we would call the variability. These are the number
18 of predicted cases, anywhere from 80 to 80,000
19 presented. Along the Y axis we present this as a
20 percentile, the frequency percentile.

21 So the 50th percentile, the expected
22 number of cases is around 200, which is the predicted
23 one in a million that you've heard before, for normal
24 CJD in this country.

25 Again, the conclusion one draws from this

1 graphical demonstration is that any risk assessment
2 that one could come up with is highly uncertain. It's
3 extremely wide in its range, and that's to be
4 expected, considering the tremendous uncertainties
5 that you're dealing with, one of the major ones being
6 the onset of the occurrence of a disease syndrome.

7 Relative to the United States: BSE has
8 not been reported in the U.S. I understand that there
9 are some that would disagree with that particular
10 concluding statement, but it is a conclusion that one
11 hears over and over again.

12 There is no beef from the U.K. that has
13 been imported into the U.S. since 1989. Gelatin, as
14 you know, has been exempted from this ban. Variant
15 CJD has not been reported in the U.S. to date.

16 Conclusions: Number one, you must define
17 the public health question you're trying to answer
18 very thoroughly. Is it a safety assessment or is it
19 a quantitative risk assessment consideration?

20 It is important to always keep in mind, as
21 Dr. DiNovi has already described, that one of the
22 major uncertainties that we're going to have to
23 grapple with is that consumption of gelatin is
24 widespread, variable, and generally chronic in nature.

25 There are a number of other uncertainties

1 that you're going to have to come to grips with in
2 terms of hazard identification -- what is the
3 etiological agent; the dose response extrapolation;
4 and the relevance of endpoints?

5 There are tremendous and significant
6 uncertainties that will have to be dealt with in any
7 safety and risk assessment paradigm, and the
8 occurrence of CJD in the U.S. is quite rare, as you've
9 heard before in your previous meeting, about one in a
10 million, and based on the current U.K. experience, the
11 risk of variant CJD is also at this point in time
12 quite rare.

13 That concludes my presentation.

14 CHAIRMAN BROWN: Thank you, Dr. Bolger.
15 Are there any questions for Dr. Bolger? Linda?

16 DR. DETWILER: Dr. Bolger, I had some
17 skepticism in the statement that BSE is not reported
18 in the United States other than speculation of
19 sporadic --

20 DR. BOLGER: No, I was just acknowledging.
21 There is a difference of opinion on that issue.
22 That's all.

23 DR. DETWILER: Well, but maybe not on the
24 reporting -- I don't know if there's a difference, but
25 there's a difference of opinion that maybe there is a

1 different form of a TSE in cattle.

2 DR. BOLGER: Right. I just wanted to
3 acknowledge that there is this endpoint.

4 DR. DETWILER: I just want to go on the
5 record to say 5,552 brains examined now, all this
6 year, brains for both histopathology as well as
7 immunohistochemistry for the prion protein, and still
8 no evidence of not only BSE or another form of TSE in
9 cattle in the United States.

10 CHAIRMAN BROWN: Yes. There are two
11 questions -- two issues. We certainly do not have a
12 BSE epidemic in the United States, by any criteria.
13 The only question is whether or not there are
14 unrecognized, rare cases of spongiform encephalopathy
15 in cattle, rare as in humans, but in humans they're
16 recognized at the one in a million level.

17 The question is: Would a similar disease
18 in cattle go unrecognized? That is unanswerable at
19 the moment, but there is certainly no evidence in
20 favor of it.

21 Any other questions for Dr. Bolger? If
22 not -- Yes, Ray?

23 DR. ROOS: I just -- When you say there's
24 no evidence in favor of BSE in this country, there was
25 one episode of transmissible mink encephalopathy in

1 which an issue had been raised up -- Is that right? --
2 of some bovine contaminated tissues?

3 CHAIRMAN BROWN: Yes.

4 DR. ROOS: I don't know whether that's
5 evidence, but at least there is perhaps the question
6 of whether there is unrecognized bovine spongiform
7 encephalopathy here, and perhaps some hints that
8 perhaps that might occur.

9 CHAIRMAN BROWN: Right.

10 DR. ROOS: Maybe sporadic.

11 CHAIRMAN BROWN: No, I stand corrected.
12 That is a major contribution, and I'm glad it gives me
13 an opportunity to mention the name of Richard Marsh,
14 who is deceased, who was really the first one in this
15 country to sound the trumpet of the possibility that
16 transmissible mink encephalopathy might not be the
17 result of exposure to scrapie but exposure to a
18 disease in cattle. Still unproven, but that is, in
19 fact, the single piece of evidence that, yes, is pro.

20 So I was wrong. There is one piece of
21 evidence for.

22 DR. HUESTON: May I -- Would I suggest
23 that that's a hypothesis rather than a piece of
24 evidence?

25 CHAIRMAN BROWN: Well, it's a piece of

1 evidence, Ken, in the sense that what seems like
2 adequate study eliminated any -- it is hypothesis, but
3 if the mink got spongiform encephalopathy as a result
4 of diet, that's the hypothesis. If they did, then
5 there is one study that indicates that the only
6 dietary source they could have had was cattle.

7 There is one such outbreak in this country
8 and another, as I recall, in Canada.

9 DR. HUESTON: I guess I might turn it
10 around a little bit. In other words, he took the mink
11 -- the TME-infected brains and inoculated cattle and
12 was able to create a disease in cattle, but there was
13 never any work in which he was able to take cattle,
14 any cattle in the United States, and inoculate mink
15 and see the disease.

16 CHAIRMAN BROWN: Yes. My comment has
17 nothing to do with his subsequent transmission
18 experiments, only the epidemiologic observations of
19 the outbreak. That is to say, there is a paper in
20 which an outbreak of mink encephalopathy occurred, and
21 the only diet -- The only diet that these mink had was
22 a diet that consisted of Downer cattle.

23 DR. HUESTON: May I just respectfully
24 suggest that, again, that was -- the recollection has
25 been challenged at time, but the recollection of a

1 producer as to the feed sources for the herd --

2 It is a hypothesis, and there's an
3 anecdotal piece of evidence that is -- or anecdotal
4 story that's published, I admit, but I think it's far
5 away from a definitive piece of evidence.

6 CHAIRMAN BROWN: Yes, anecdotal in the
7 sense that it's a single observation, but that was the
8 point that was raised. There is this single
9 observation and, for what it's worth, it's a solid
10 observation. The main thing is, I suppose, you're not
11 sure that the mink got it from anything in their diet.
12 You just don't know. I mean, that's unproven.

13 Okay. We now have a short presentation by
14 Dr. John Gray about USDA regulations on the
15 importation of gelatin.

16 DR. GRAY: I'm John Gray, Senior Staff
17 Veterinarian with the Import/Export Products Staff.

18 I would like to mention that within AFAS,
19 veterinary services, our authority relates to animal
20 diseases and, therefore, our regulations normally
21 reflect this. Up until the time that BSE was
22 recognized and reported, we did not regulate gelatin,
23 because, as you have heard earlier this morning, the
24 processing of gelatin is a most destructive process
25 for most living organisms.

1 At the present time, we have two ways for
2 gelatin to be imported into the United States. One is
3 by a permit issued by our section, and this is used
4 for gelatin coming from BSE affected countries, and
5 our regulations do not permit this gelatin to be used
6 for animals, animal pharmaceuticals. It is mainly for
7 industrial, for other uses.

8 Then since gelatin is a very large product
9 for being imported and there are many countries that
10 it comes from, we now require a certificate of origin
11 for gelatin coming in from non-BSE affected countries,
12 and the certificate of origin must be endorsed by the
13 veterinary service of the country where the gelatin is
14 manufactured, relating to the species and the
15 processing of the product.

16 This, basically, is the regulations we
17 have. I have copies for your committee, if you would
18 like them. That's all I have for you.

19 CHAIRMAN BROWN: Thank you, Dr. Gray. Any
20 questions for Dr. Gray? We have this sheet that
21 everyone on the committee will have a copy of.

22 Yes? Dr. Wolfe?

23 DR. WOLFE: Dr. Gray, you said that up
24 until the time of the BSE outbreak in the U.K. that
25 you didn't do any regulation. Could you just -- I

1 assume that, once this regulation was promulgated,
2 there was some statement of reasons. Could you just
3 briefly describe exactly why at whatever point, 1987
4 or --

5 DR. GRAY: Well, at that particular point
6 in time, there was very little evidence of what
7 products might or might not transmit the disease
8 agent. So the regulations were promulgated on
9 reducing any existing risk that could cause us
10 problems in our livestock population.

11 DR. WOLFE: But did it apply just to
12 gelatin or to other kinds of imported products?

13 DR. GRAY: Oh, we have other regulations
14 related to animal products, yes, for BSE.

15 DR. WOLFE: But that started at that time?

16 DR. GRAY: Correct.

17 DR. WOLFE: That's really my question.

18 DR. GRAY: Oh, yes. We have a whole other
19 section relating to rendered products and glands and
20 organs and --

21 DR. WOLFE: And in each case it's the
22 country of origin, species, and the processing
23 certification?

24 DR. GRAY: Yes.

25 CHAIRMAN BROWN: And again, what was this

1 date?

2 DR. GRAY: It probably was -- We did it by
3 policy probably for a year before we promulgated
4 regulations, because we had very broad authority, and
5 the Secretary of Agriculture can designate or delegate
6 down to us, and we can enact restrictions before we
7 promulgate the regulations.

8 CHAIRMAN BROWN: Any other questions for
9 Dr. Gray? Yes, Bob?

10 DR. ROHWER: Could you just speak to the
11 issue of which products are under your jurisdiction
12 versus FDA jurisdiction, and who -- you know, AFAS
13 controls --

14 DR. GRAY: When it comes to animal
15 diseases, we don't have limitations on us. There are
16 many times FDA and the USDA will jointly have
17 responsibility for certain products, but ours will
18 always relate to animal diseases.

19 DR. ROHWER: But, for example, do your
20 regulations apply to, say, processed food that's
21 imported to the United States that contains gelatin?

22 DR. GRAY: -- processed food can possibly
23 carry disease agent and that it could come in contact
24 or exposed to the national livestock population, yes.
25 We do this with TV dinners that are partially cooked,

1 particularly from foot and mouth disease countries.
2 We do it with swine or pork products from countries
3 that have African swine fever, swine vesicular
4 disease, hog cholera.

5 DR. ROHWER: How about pharmaceuticals for
6 humans?

7 DR. GRAY: We also do that for
8 pharmaceuticals, because many of them are either
9 correctly or incorrectly used in animals.

10 CHAIRMAN BROWN: Yes?

11 DR. HUESTON: Just, Dr. Gray, one other
12 point for clarification. In terms of raw materials
13 coming in for gelatin production in the United States
14 -- so bones or hide trimmings entering the U.S. for
15 use in gelatin manufacture -- are they currently
16 covered by USDA?

17 DR. GRAY: Yes. In fact, all bones,
18 regardless of what they're coming in for, if they are
19 going to be grilled or further processed in any way,
20 must enter the United States under one of our import
21 permits.

22 DR. HUESTON: And are bones allowed from
23 BSE-affected countries?

24 DR. GRAY: The only exception are the
25 highly processed bones for bone china.

1 DR. HUESTON: Just to make sure I
2 understand correctly, so you're saying the only bones
3 that could come in from BSE-infected countries would
4 be bones that are highly processed for bone china?

5 DR. GRAY: Correct.

6 DR. HUESTON: So that bones that were
7 coming in from BSE-affected countries, say, to go into
8 gelatin manufacture would not be allowed -- would not
9 be permitted?

10 DR. GRAY: No.

11 DR. HUESTON: And how about hide
12 trimmings?

13 DR. GRAY: Hide trimmings -- We basically
14 let hides in from BSE countries, but we do not let the
15 trimmings go into rendering.

16 DR. HUESTON: One last question: Do I
17 understand it correctly in reading this that
18 essentially the permittee is -- or the applicant is
19 required to show a certificate that also attests to
20 the origin of the animals from which the material is
21 derived?

22 DR. GRAY: Correct.

23 DR. HUESTON: So if it was bones -- For
24 instance, if it were bones coming in from country X,
25 that that certificate would attest that those bones

1 did not originate from a -- essentially, that those
2 bones originated from the country of origin or from
3 another country that was not affected by BSE?

4 DR. GRAY: That is correct, and we would
5 not take that statement from the manufacturer. It
6 must come from the government veterinary service who
7 has the responsibility for animal health.

8 DR. HUESTON: Thank you.

9 CHAIRMAN BROWN: Yes?

10 MR. FAITEK: I'm a little confused. On
11 one of the slides from this morning, it showed that
12 approximately 3,000-4,000 tons of bovine bones were
13 used in gelatin, but you just said that they're not
14 allowed to be imported. Where did those --

15 DR. GRAY: From BSE affected countries.

16 MR. FAITEK: Well, I thought those were
17 from BSE affected countries.

18 DR. GRAY: No, I believe those are from
19 Argentina.

20 CHAIRMAN BROWN: No, I know what you're
21 talking about. There was a slide which showed that
22 there were 3-4,000 pounds or tons or something, some
23 weight -- metric tons, but I think that was gelatin
24 per se, was it not, not the bones? I'm not sure.

25 It was gelatin, right.

1 DR. GRAY: And gelatin would be permitted
2 in the country under certain conditions.

3 CHAIRMAN BROWN: Right. So it was not the
4 bones that were imported. It was the gelatin, and a
5 small proportion of that came from BSE -- so called
6 BSE countries.

7 Other questions? Then we shall go right
8 on to hear Dr. Robert Rohwer from the VA Medical
9 Center in Baltimore talk about the survivability of
10 TSE agents and the kinetics of inactivation.

11 DR. ROHWER: Paul, I was counting on the
12 break to load my slides.

13 CHAIRMAN BROWN: Ah. Would you like to
14 follow Carol Vincent, in that case, or how much time
15 do you need, Bob? We'll follow the schedule.

16 Now that we have a couple of minutes, any
17 other questions for any of the previous three speakers
18 that anybody has not yet asked? Yes?

19 DR. WOLFE: Paul, again for Dr. Gray,
20 based on the certification that you look at when you
21 look at this country of origin species or what-not,
22 have you compiled any data that says what percentage
23 of the gelatin is coming from which country, which
24 species or whatever? I mean, we're going to
25 supposedly hear something else, but do you keep tabs

1 on this stuff?

2 DR. GRAY: No.

3 DR. WOLFE: No?

4 DR. GRAY: Congress may or a foreign
5 agriculture service may, but we do not.

6 DR. WOLFE: You don't know whether they
7 do?

8 DR. GRAY: No. I haven't tried to look it
9 up. Relating to this, you might be interested in
10 knowing that our agency, AFAS, does have 2,000
11 inspectors out at the ports where products come in,
12 and we do examine the products, and we have very good
13 working relationship with Customs where products like
14 gelatin will be put on an automatic hold until
15 Agriculture has reviewed the paperwork and decided if
16 it's a legal entry or not.

17 DR. WOLFE: But even at the inspector
18 level, there's no records kept that would be able --

19 DR. GRAY: No.

20 CHAIRMAN BROWN: Yes?

21 DR. BOTSTEIN: I'm Dr. Paul Botstein from
22 the Center for Drugs at the FDA. I have a question
23 about the USDA certificates. Do they give only the
24 country in which the cow has most recently resided or
25 do they give information about previous places the cow

1 might have come from?

2 DR. GRAY: They are supposed to give where
3 the cow basically has been a resident of. Our
4 regulation -- and of course, everything has a
5 practical level of enforcement, but if an animal has
6 been in one of the countries that is affected with
7 BSE, it is not allowed to be in the product, and this
8 will depend partly upon the identification and the
9 tracing within the countries.

10 DR. BOTSTEIN: But the certificates would
11 list every country a cow has been in?

12 DR. GRAY: No. It would list the one, the
13 most recent one where it's supposed to have been a
14 resident of.

15 CHAIRMAN BROWN: Bob?

16 DR. ROHWER: I was asked to address two
17 topics in the course of this meeting. The first
18 concerns inactivation of these agents, and what we
19 know about that. Then the second was validation.

20 I have a feeling that it might have been
21 more effective to have combined these two things and
22 addressed both these topics at once, but this is the
23 way it turned out. So that's the way we'll go about
24 it.

25 Just by way of introduction, this is a

1 list of properties of these agents, about which I
2 think there's general agreement, even though there is
3 a lot of controversy in this field. They are fatal
4 central nervous system diseases with this very long
5 subclinical incubation which makes detection very hard
6 and makes eliminating these diseases almost impossible
7 from the standpoint of culling.

8 The issue that we're going to talk about
9 this afternoon is this one, disinfection. They are
10 extremely difficult to disinfect, and in fact,
11 disinfection requires destructive methods. Moreover,
12 if one wants to use physical methods for removing
13 them, there is an issue about what the actual size of
14 these agents are and what would be an appropriate
15 method.

16 We can trace almost all of our problems
17 concerning these agents to failure to disinfect, and
18 the most dramatic of those failures, of course, has
19 been the BSE epidemic. This was a failure at the
20 level of rendering to remove this material from feed,
21 and we have ended up with this epidemic here, and now
22 we've got the origins of potentially another epidemic
23 in people in variant CJD, ultimately related to the
24 same issue.

25 There have been other sources of failure

1 of disinfection. The most important one is human
2 growth hormone, and the number of HGH cases associated
3 with human cadaveric pituitary derived human growth
4 hormone is approaching 100 cases. It's up in the
5 eighties, I think.

6 Gonadotropin -- there have been a few
7 cases from the same source; and dura mater, another
8 tissue that's obtained from brain of human cadavers,
9 has -- the number of cases reported associated dura
10 mater doubled in the last few weeks with the
11 announcement by the Japanese that they have discovered
12 30-50. It's not quite clear to me yet how many cases
13 -- new cases associated with this material.

14 Then there have been a scattering of cases
15 associated with surgery, corneal transplant, deep
16 penetration electrodes, etcetera.

17 In animals there was a formalin fixed
18 vaccine that was prepared in the forties to louping
19 ill disease, a flaky virus disease. Unfortunately,
20 the vaccine was prepared in the brains of sheep which
21 were not known at the time to be harboring scrapie,
22 but several thousand scrapie infections were
23 ultimately traced to that vaccine distribution, and it
24 resulted in a high incidence of scrapie in Scotland,
25 which has lasted to this day.

1 Transmissible mink encephalopathy --
2 that's also food borne. Then of course, there's --
3 and there's always been some question about where
4 sporadic CJD comes from, and one of the possibilities
5 has always been that it's through an exposure that has
6 to do with some failure, either of an iatrogenic
7 source or in food processing or something like that.

8 The methods that are required for
9 sterilization of these agents, the recommended
10 methods, are 132 degrees Centigrade after 60 minutes
11 in a gravity displacement autoclave or the U.K. and,
12 I believe, E.C. has also adopted this standard of 134
13 degrees Centigrade for 30 minutes -- actually, it's 18
14 minutes in a force load autoclave, slightly different
15 methods of autoclaving, both methods highly effective
16 usually.

17 Sodium hydroxide is also very effective in
18 removing these agents. 1 Normal sodium hydroxide for
19 60 minutes is essentially sterilizing. You can
20 challenge this material or these methods in such a way
21 that you can get animals that survive.

22 Incineration is presumed effective. We
23 all hope it's effective, because a lot of BSE material
24 is being incinerated in Britain as a method of getting
25 rid of it. It has not, to my knowledge, actually been

1 validated.

2 Hypochlorite 5% has been shown to be quite
3 effective in David Taylor's hands. However, the
4 efficacy of these methods depends a lot on the
5 methodological details, and when people try to push
6 the system as hard as they can, there have been some
7 notable failures.

8 The concern here is how robust are these
9 methods, and what is the actual margin for error, and
10 how much does it depend upon context of the
11 sterilization?

12 In my hands, 121 degrees Centigrade under
13 pressure kills 6 logs of infectivity upon contact with
14 those temperatures. These were very carefully
15 conducted experiments. Samples were well homogenized,
16 placed in serum bottles, and the inactivation was
17 actually done in an oil bath so that they could be
18 removed quickly for assay.

19 In other experiments, placing brain
20 homogenate, for example, in petri dishes and
21 autoclaves we have also obtained high levels of
22 inactivation, but occasionally out here even at 60
23 minutes there will be a survivor among the animals
24 receiving the undiluted inoculum.

25 David Taylor has performed a number of

1 experiments in the last couple of years in which he
2 has seen quite significant survivals after treatments
3 at these same very high temperatures, 130 -- this is
4 untreated, 19 out of 19 animals inoculated with
5 undiluted inoculum came down, as you would expect; but
6 134 degrees at 18 minutes -- this is European standard
7 -- four out of 13; 134 for 30 minutes, four out of 26;
8 134, 60 minutes, 14 out 22. Here's a -- This was an
9 experiment in which the challenge was to let the
10 autoclave fluctuate in a way in which any well
11 validated autoclave would not, and amazingly he got 19
12 out of 19 survivors there.

13 Well, what's going on here, and what's the
14 difference between these two experiments, and what can
15 this kind of data tell us?

16 The experiments that I did were -- They're
17 really the ideal gas version of sterilization by heat.
18 I was interested in what are the intrinsic properties
19 of the agent itself upon exposure to these kinds of
20 temperatures.

21 We used a 10% brain homogenate that was
22 highly homogenized by sonication, sealed into bottles.
23 The whole thing was done with constant stirring,
24 thermistors recorded to temperature of the stuff. We
25 know exactly what was going on there.

1 We got very high levels of inactivation,
2 in fact total inactivation by 60 minutes, of the input
3 challenge at the 121 degrees. On the other hand,
4 Taylor was using much higher temperatures, but his
5 challenge was a worse case challenge.

6 He was using whole brain that had been
7 mushed up and macerated. There was no dilution
8 whatsoever. It was stuffed into a long neck tube,
9 autoclaved, and the process was static.

10 Now what do these survivals tell us about
11 what we're dealing with here? A point I want to make
12 is that it says nothing about the issue about whether
13 these diseases are caused by viruses or prions. These
14 are methods which kill viruses and destroy PrP
15 resistant protein in each case.

16 As a consequence, the nature of the
17 survival doesn't really have anything to do with the
18 agent. It has something to do with the context of the
19 agent.

20 By looking at the ideal case, we know that
21 the agent itself is not intrinsically resistant.
22 There's some problem with the delivery of the
23 inactivant that's creating the survival, because you
24 can change the rate of survival simply by how you
25 present the agent to the inactivant.

1 What are the nature of these survivors?
2 Well, there's been -- One possibility, of course, is
3 that we selected out a heritable intrinsic -- a
4 population with an intrinsically different
5 susceptibility. However, where this has been looked
6 at -- and it hasn't been looked at very much but there
7 are a couple of instances where people took the
8 survivors of a process like this and grew them up
9 again and re-treated them -- it doesn't look like it
10 has anything to do with heritability.

11 Aggregation is a possibility, especially
12 in the case of the Taylor experiment where he was
13 looking at just brain mush, but myself, I favor the
14 idea that there's some sort of compartmentalization
15 that's going on here.

16 These experiments by our Chairman may
17 provide some insight as to the differences. It turns
18 out that these agents are quite resistant to dry heat
19 sterilization. This is log₁₀ reductions. This is
20 derived from the data in this experiment.

21 At 160 degrees for 10 minutes, there were
22 two to three logs of reduction from whole brain, from
23 purified fibrils, the amyloid component of brain,
24 having three logs; 160 degrees, 60 minutes, a little
25 more activation; and 360 degrees for 60 minutes, quite

1 significant inactivation. However, it is important to
2 note that there were still survivors even after this
3 treatment right here.

4 The number of survivors -- The level of
5 survivors here is quite high, 10^5 or so, fourth or
6 fifth, and this is not terribly surprising. There is
7 quite a literature, a surprising amount that comes out
8 of NASA when they were investigating survival of
9 microbes on moon rocks, and they were scraping things
10 off of rocks in the Mojave Desert and that kind of
11 thing, to see what they could get.

12 There are organisms that can survive dry
13 heat conditions, quite high dry heat conditions,
14 though of I know of no experiments actually looking at
15 this temperature.

16 What it suggests is that perhaps what's
17 happening here is that, in the process of pushing this
18 into a tube and slowly bring it to temperature in an
19 autoclave, we're drying some of the material on the
20 wall of the tube, and that stuff is actually being
21 exposed to those temperatures under anhydrous
22 conditions, not under hydrolytic steam conditions, and
23 that's the nature of the survival.

24 It could be something else as well. Brain
25 is full of fat, and this material is hydrophobic. If

1 it's embedded in the fat or encapsulated in some way,
2 it may also be able to protect itself from steam.

3 What we do know is that in a well
4 homogenized, well presented, well controlled
5 situation, we can, nevertheless, remove most of those
6 sanctuaries and kill most of this agent. The converse
7 of that is that in any situation where you're relying
8 on these inactivation methods for removing these
9 agents, they almost always require some sort of
10 validation to make sure that it actually works under
11 the conditions that are being employed and in the
12 presence of the materials that are being employed.

13 I want to make one other point about this
14 experiment before we move on. That is that this was
15 a kinetic experiment. We were interested in the rate
16 of inactivation of these agents at this temperature.

17 In fact, what we see is that -- This was
18 surprising at the time that I did it, actually -- the
19 inactivation all occurred within point of contact with
20 these temperatures. The very first sample I took
21 after the material reached 121 degrees, already we had
22 six logs of inactivation.

23 It took a few minutes more, about ten
24 minutes, to get rid of the last bit of the measurable
25 infectivity in this assay, but the vast majority of it

1 occurred quickly.

2 That tends to be the case for an awful lot
3 of -- There's very limited data on the kinetics of
4 inactivation of these agents, but where it has been
5 done -- and I'll show you some more in a little bit --
6 what you see -- what you're going to get, you get
7 fairly quickly, and then there are -- there's a
8 residual subpopulation which survives a further
9 inactivation or inactivates at a much slower rate.

10 This is not an unfamiliar phenomenon in
11 virology. It's something that has plagued water
12 purification and people who make killed vaccines, for
13 example, for decades. It's just that these agents are
14 -- The size of the population that escapes is
15 sometimes -- is somewhat greater than you might see
16 for other viruses.

17 It's important to keep this in mind, that
18 this initial rate of inactivation represents how the
19 majority of the population is behaving. 99.9 percent
20 of the stuff is killed in the first few minutes of
21 inactivation. That's the majority of the population.

22 From the standpoint of a chemist, this is
23 the type of data -- it's the rate of inactivation
24 that's important for producing the physical properties
25 of the agent, the intrinsic properties of what you're

1 talking about.

2 On the other hand, disinfection and
3 sterilization, the goal of this, is to kill the most
4 resistant member of the population. In the case of
5 these experiments on steam sterilization, that parts
6 per billion, parts per hundred billion, but still it
7 only takes one of those guys to cause an infection,
8 and if he's found a place to hide, he's a problem.

9 On the other hand, this surviving
10 population does not reflect on the structure of the
11 majority population of the agent.

12 Now actually I wanted the overhead for a
13 minute, and then we'll go on to this slide.

14 There are two steps in the gelatin
15 manufacturing process that harbor some prospect of
16 killing these agents. One is the thermal inactivation
17 -- the thermal exposure that occurs at the end.

18 I'm very curious about that, because --
19 and the reason I asked my question earlier is that the
20 data that I just showed you, that kinetic curve,
21 showed that you don't need to see that temperature for
22 very long to get significant inactivations.

23 Of course, this is something that would
24 have to be validated under the conditions that it's
25 actually performed by the industry, and it's important

1 to know whether those temperatures actually reflect
2 high temperature or high pressure steam or whether
3 they're an atmospheric pressure, and that's still not
4 exactly clear to me from the answers I got earlier.

5 The other area that offers some hope is
6 inactivation by sodium hydroxide. This is an
7 experiment that I performed years ago in collaboration
8 with Paul Brown, and looking at the sensitivity of the
9 CJD agent and scrapie agent to sodium hydroxide.

10 It's one of a large number of experiments
11 which I'll show you in a moment, but basically --
12 again, this was done on fairly refined -- It's brain
13 homogenate, but it's well homogenized material, and
14 the experiments were -- the sampling and that sort of
15 thing was done very carefully.

16 What you see here is that 1 normal sodium
17 hydroxide is highly effectively, most of the killing
18 by 15 minutes. By 60 minutes we're at the titration
19 limit, which means that that's all the infectivity we
20 put in there, and by 60 minutes in the scrapie case
21 we're at the titration limit again.

22 Kent normal is almost as effective, though
23 it didn't remove all of the infectivity; whereas, 100th
24 normal, even at an hour, is not showing anywhere near
25 the same level of removal of infectivity as the higher

1 concentrations.

2 With respect to the gelatin process, just
3 rule of thumb, approximately anyway, pH of the
4 negative logarithm of the hydrogen ion concentration,
5 and so 1 normal sodium hydroxide has a pH of 14-13-12,
6 and the slike-line process are working between here
7 and here; i.e., they're working in the borderline of
8 efficacy for this type of treatment.

9 On the other hand, neither I nor anyone
10 else until this validation was done that, I believe,
11 Mr. Schrieber will talk about in a moment, had ever
12 looked at an exposure of, you know, days and days and
13 days, 30 days, 45 days, 60 days. If this was a rate
14 exposure extended 60 minutes per hour -- I mean 1 log
15 per hour over that period of time, you might expect
16 very large inactivations.

17 On the other hand, we may have reached
18 some sort of plateau, and that remains to be seen or
19 determined.

20 Now I want to go back to the slides, and
21 that will be all for the overheads.

22 Now it turns out that there's quite a
23 literature on exposure to sodium hydroxide, and I'm
24 not asking you to look at the details of this slide,
25 because you probably can't see it. All I want you to

1 know is there's a lot out there. A lot of people have
2 gone back and looked at this in various ways.

3 The important points I want to point out
4 here is that 1 normal is highly efficacious. However,
5 there are people who are doing the experiment in ways
6 in which they are getting results that differ from our
7 own, and there are significant survivals even after an
8 hour or two hours sometimes being reported for sodium
9 hydroxide.

10 So again, it's important to consider the
11 context and to validate these methods, if you're going
12 to rely on them.

13 What's happening here: It's again, I
14 believe, a situation of context of the presentation.
15 If the reagent can't reach the infectivity, it can't
16 kill it. If you stuffed your brain homogenate in a
17 little plastic bag and sealed it and thrown it into
18 sodium hydroxide, nothing will happen.

19 Is there a molecular level at which this
20 is happening with these agents? Is there the
21 potential for that? There must be, because that's
22 what we're seeing, and perhaps it's material that's
23 being trapped in micelles or something like that, but
24 really we don't know.

25 Is there a potential for this kind of

1 thing? There certainly is. This is a picture of an
2 amyloid plaque from a GSS brain. The infectivity in
3 this disease is closely associated with this material.
4 Here's an electron micrograph of the fibrils that make
5 up that plaque.

6 Whether you think that the infectivity is
7 associated with these little spheres which seem to be
8 always present in these kinds of preparations, some
9 adventitiously associated virus, or its the fibrils
10 itself or its some subunit of the fibril,
11 nevertheless, the opportunities for associations and
12 perhaps sanctuaries against these type of procedures
13 are quite abundant in material of this sort; and as a
14 consequence, maybe we shouldn't be so surprised to see
15 the kinds of things we're seeing.

16 Aggregation: This -- It's well known that
17 these agents tend to aggregate. It's something that
18 has bedeviled attempts to purify and characterize them
19 over the years. Aggregation is something that has to
20 be considered and has to be controlled in any type of
21 validation work, because when you take several active
22 infectious particles and glob them together in one
23 piece and that becomes your inoculum, you effectively
24 reduce the titer without having done anything to the
25 agent itself in terms of killing it or removing it.

1 So it can be very dangerous, if it's
2 unrecognized and you draw the wrong conclusions about
3 removal, when actually what you're talking about is
4 aggregation. Aggregates can also be unstable, which
5 means that you can remove infectivity from one part of
6 the process and then find it again later when they
7 come apart due to a change in pH, temperature, buffer
8 or what have you.

9 There are other things that can be used to
10 inactivate these agents. This list right here:
11 Strong chaotrophs, phenols, various phenols, phenol
12 extraction for sure with just phenol. Some detergents
13 have some potential for inactivation, some lipophilic
14 solvents. In general, protein denaturants have -- are
15 efficacious in removing these things.

16 Frequently -- and this usually happens by
17 serendipity -- combinations of agents can also be far
18 more effective than any single inactivant by itself
19 and, of course, when one is looking at ways to extend
20 the potential for things like this to kill these
21 agents, it's always worth -- if your product can
22 withstand the treatment -- to explore greater
23 exposure, either by time or concentration.

24 For something like gelatin, it's
25 conceivable that one could build in a virus removal

1 step into the process, which would perhaps provide a
2 great deal of additional assurance in terms of the
3 removal of these agents, but it's something that would
4 require research and development.

5 Just thought I'd give you a few more
6 examples of inactivants. These are not things that
7 really are practical, necessarily, for industrial
8 production, but there are some lessons that can be
9 learned here.

10 This is an inactivation in sodium
11 hypochlorite -- bleach, in other words, half-percent
12 bleach. This is the scrapie inactivation, and these
13 are other viruses which were added as controls. The
14 point I want to make here is this is the surviving
15 fraction with time of exposure. The next three graphs
16 will be of this sort.

17 So what you see is that you have almost
18 instantaneous killing down to the 3 log level and then
19 a slower rate of killing after that. You see
20 something similar for other viruses. Those were added
21 to the system at the same time. Available chlorine
22 state, pretty much constant for the course of this
23 experiment.

24 These viruses right here were added both
25 in the presence of brain homogenate and in highly

1 purified form in PBS. In PBS they were killed to much
2 higher levels very rapidly, suggesting that there are
3 places in a complex mixture like this for even
4 conventional viruses to find a sanctuary from the
5 reagent.

6 There are reagents like sodium
7 metaperiodate. There are viruses which are more
8 resistant to this treatment than the scrapie agent,
9 which is right here. Here are some of the other
10 members of this population. The closed symbols
11 represent things in the presence of brain homogenate,
12 and the open symbols represent the same viruses in
13 highly purified form.

14 Finally, the point of this slide is that
15 here's an example where the rate of inactivation of
16 scrapie infectivity seems to have changed really upon
17 dilution, going from 10 percent brain to one percent
18 brain, and the lesson there is borne out from a rather
19 limited but still probably significant literature
20 which suggests that, as you refine the infectivity to
21 higher and higher levels, it does -- its sensitivity
22 to some of these reagents at least increases.

23 What happens with highly penetrating
24 inactivants like ionizing radiation? Well, here we
25 don't see any hint of this, and that's exactly what

1 you would expect. There is no sanctuary from ionizing
2 radiation, and that's why it is such a highly favored
3 approach to sterilization of complex mixtures.

4 On the other hand, this radiation data has
5 often been used to make -- to claim at least that the
6 scrapie agent has a subviral size and, therefore,
7 could not be a virus. This -- I presented this merely
8 to make the point that, if you extrapolate the rate
9 constant for inactivation of these agents for scrapie
10 compared to other viruses, that in fact it falls into
11 the range of the smaller viruses, but viruses,
12 nevertheless.

13 This is an important consideration if
14 we're going to use size as a method for removing
15 infectivity. It would be nice to be able to use this.
16 Viral filtration is not at a -- has not come as far as
17 it could, but I think we can expect over the next
18 decade or so for there to be some really significant
19 advances in this area; and if we could use
20 nanofiltration of some sort to remove this material,
21 it would be extremely useful, but the size of these
22 agents is disputed, and from the ionizing radiation
23 data the target calculation, which is a very old but
24 honored way of analyzing this data, gives a subviral
25 size, very small size. The standard curve gives

1 something that's more in the range of possibility for
2 real viruses.

3 Filtration studies themselves seem to
4 suggest -- track etch filters anyway seem to suggest
5 a size between 30 and 50 nanometers. This is
6 something that would be quite useful, if it's true,
7 for removal purposes.

8 On the other hand, there are some reports
9 using ultrafilters that the stuff is passed 100,000
10 dalton cutoff membranes. It has a very small
11 sedimentation velocity, but that's consistent with a
12 small virus or a large protein.

13 Finally, there have been various
14 chromatographic methods that have been used to -- Size
15 exclusion of various sorts have been used to try to
16 size the agent, and the results have been variable
17 from molecular to quite large, and that probably has
18 something to do with technical problems with the
19 experiments themselves.

20 Just a couple more points: In processing
21 these agents, you have to distinguish between methods
22 that kill and methods that sequester. All of these
23 things can be highly effective in terms of removing
24 these particular agents.

25 That is because they are hydrophobic.

1 They are adherent. They tend to stick to surfaces.
2 If the surface area that they're presented with goes
3 up, they can even stick to very large portions of the
4 matrices and significant losses will be detected in a
5 validation.

6 Of course, this presents problems, because
7 the stuff is not actually killed. It's now in your
8 infectious waste or it's still in your process stream
9 attached to something else, and that brings up the
10 issue of the necessity for between-batch cleaning and
11 things like that, if you're actually trying to manage
12 exposures to these agents.

13 Now a couple of take-home slides. What
14 are our recommendations? It's clear that these agents
15 can be killed by things like steam. 121 degrees is
16 enough, but 132 or 134 degrees gives a much wider
17 margin for error; and because of the sensitivity of
18 the inactivations to the context of the agent,
19 wherever we can get a margin for error, we should take
20 it, but optimize sterilization of these agents.

21 They need to be well dispersed.
22 Surfactants may be helpful. Homogenization is
23 certainly helpful. One of the troubling features of
24 the gelatin manufacturing process is that the steps --
25 even the sodium hydroxide steps -- not sodium

1 hydroxide, but the lime steps are performed on
2 material that's chunked and particulate. That's not
3 the way we want to have it, if we could do it ideally.

4 Finally, these types of dispersal
5 eliminate sanctuaries. Agitation is helpful to make
6 sure everything gets exposed.

7 Finally, as materials become more and more
8 refined, the potential for protective associations
9 goes down, and the potential for inactivation goes up.

10 Device sterilization -- I've included
11 this, not because we're talking about devices
12 necessarily, but some of the things that have worked
13 for us in the laboratory at least is to immerse things
14 during steam sterilization. Then you know you're
15 getting contact with hydrolytic aqueous environment at
16 those temperatures.

17 It's always to combine two or more methods
18 in the laboratory. Wherever possible, we use sodium
19 hydroxide followed by steam sterilization or combined
20 together at the same time, if the materials can take
21 it.

22 Then these are other issues which are not
23 very pertinent to this discussion, and I'll stop
24 there.

25 CHAIRMAN BROWN: Thank you, Dr. Rohwer.

1 Perhaps we can go on to hear Carol
2 Vincent, and then have some questions.

3 MS. VINCENT: I'm Carol Vincent with the
4 Center for Drugs in the Food and Drug Administration.

5 I know you've heard an awful lot about
6 gelatin so far today, but I don't think anyone has
7 really given you a particular reason why CDER is
8 interested in gelatin manufacture.

9 I'm part of the agency working group, the
10 multi-center agency working group that's been in
11 existence since '92, and we disbanded for a while, and
12 then reformed again this past year. We've had a
13 continued awareness and interest in the BSE situation
14 for a number of years, and reformed this group in the
15 past year.

16 Newer information indicates it's not yet
17 time to reduce our interest. I'm specifically
18 referring to the 16 cases of VCJD announced last March
19 and the recent diagnosis and announcement on March 21,
20 '97, of cases of BSE in the native cattle in the
21 Netherlands.

22 There are too many unknowns in this area.
23 Even though we do agree with Dr. Brown that the risk
24 is very low, there's still possibly a risk present.
25 We feel it's prudent to be cautious and err on the

1 side of caution.

2 So what is the regulatory context for the
3 MTA to look at gelatin manufacture? Well, we have
4 some definitions, and I'll try to see how gelatin fits
5 into these, and what is FDA's regulatory authority to
6 look at pharmaceutical gelatin.

7 Could I have the next slide, please.

8 So I have some definitions here, because
9 not everyone is as completely familiar with the CFR as
10 some of us might be. If you want to define a drug, a
11 specific section in 21 CFR Section 210, it's something
12 that's diagnosed for -- A drug is an article intended
13 to be used in the diagnosis, cure and mitigation,
14 treatment or prevention of disease in man or other
15 animals. That's in the Food, Drug and Cosmetic Act.

16 Next, please. If you remember, we
17 mentioned earlier a letter from December of '93 from
18 Dr. Handly to the CDER, CBER and CDRH regulated
19 manufacturers that mentioned that the use of bovine
20 materials from BSE countries might consider the
21 regulated product to be adulterated.

22 The definition of adulteration is under
23 Section 501 of the Act, and a drug or device is deemed
24 adulterated if the method used and/or facilities and
25 controls used for its manufacture, processing,

1 packing, holding do not conform or -- next slide,
2 please -- do not conform or are not operated,
3 administered in conformity with current good
4 manufacturing practices.

5 There are four words here in bold:
6 Identity, strength, quality, and purity. These four
7 words in various orders appear throughout the Code of
8 Federal Regulations pertaining to food and drugs. We
9 draw a lot of strength -- or a lot of regulatory
10 authority on these four words, particularly on the one
11 for purity.

12 Go to the next one quickly. The CGMPs are
13 defined at 21 CFR 211. Go on to the next two slides,
14 please, and the next.

15 There are a number of places where we can
16 ask for additional information. These will go pretty
17 rapidly now. This is the citation for the
18 investigative new drug application where you have a
19 specific section addressing chemistry, manufacturing
20 and controls.

21 Next, please.

22 Within that you have two specific sections
23 defining a drug substance and a drug product. We have
24 strength, identity, quality, purity again. Gelatin is
25 neither a drug product nor is it a drug substance.

1 Next slide.

2 We have an additional provision to ask for
3 additional advice or information concerning a drug
4 product at anytime.

5 The next one real quickly covers the
6 content and format of a drug application. Again, you
7 have another legal provision for substance and
8 product.

9 The next slide discusses drug substance
10 again with your identity, quality, purity and on. We
11 also have the next slide that gives the same type of
12 information on drug product, and the last of these
13 pieces of the CFR cites a particular citation for
14 special testing requirement on the next slide, which
15 most people interpret as a requirement for a sterility
16 test. This isn't true. The requirement is for a drug
17 product reported to be sterile will have a laboratory
18 test.

19 Now no one has ever required gelatin to be
20 sterile, at least in some context. It certainly isn't
21 the injectable product. We're talking about bulk
22 gelatin and the pharmaceutical gelatin.

23 That slide is a little too early, if you
24 pull that back for a moment.

25 All right. When a group of

1 microbiologists in CDER do reviews for microbiological
2 quality and sterility assurance for new drug
3 applications, investigative new drugs and supplemental
4 drug applications for the 14 medical divisions in
5 CDER, our group, together with the microbiologists in
6 the Office of Generic Drugs who perform similar
7 reviews for generic drug applications and supplements,
8 and the review scientists in the Center for Veterinary
9 Medicine wrote a guideline for these parts of CDER and
10 CVM regulated industry.

11 We conducted a number of workshops to
12 provide sterilization process validation information
13 in Chicago, San Diego, Gaithersburg -- Brussels or
14 Rome. This was to provide the applicants with the
15 type of information necessary to get more rapid work
16 through the system.

17 So the first slide on the FR. Okay.
18 December 3, '93, is the publication of the
19 sterilization process validation guideline where the
20 citation is repeated on the next slide at 58 F.R. --
21 No, that's all right -- 58 F.R. 63966, which was later
22 published as this guideline when we used the blue
23 covers, and as soon as that was out, Madigan decided
24 to reissue everything as a guidance on the next slide.

25 All right. So now this is the guidance.

1 It's still no difference in my mind from a guideline,
2 and I still tend to slip and call it that. This
3 particular one is joint between CDER and CVM.

4 Why am I talking about that? Because
5 there's a particular paragraph within this that gives
6 the justification of the style and the reason, and how
7 to go about doing process validation. We are not
8 going to go into the details of that.

9 Skip over the next slide, please, and go
10 on to gelatin, number 2247 in the corner. There.

11 None of those definitions I gave you
12 before cover gelatin. Nothing in the new drug
13 regulations covers gelatin. Gelatin -- this is its
14 definition from the USP. The USP is United States
15 Pharmacopeia. So that's the official monograph from
16 the USP. It's on page 2247, current USP.

17 Gelatin is a compendial product. By being
18 a compendial product in the Center for Drugs, it's
19 treated -- and it's nearly the same fashion as one
20 would consider a GRAS substance, generally regarded as
21 safe, except we don't use that term in CDER.

22 So this is a very, very brief definition
23 of gelatin, according to the USP, and any manufacturer
24 of a drug product can use gelatin, USP, and there's
25 really not much reason to ask them further about this

1 until the last several years where we became more
2 interested in these products.

3 You have a very minimal amount of
4 microbial information at the bottom of this. They
5 need a count less than 1,000 per gram, and it's to be
6 salmonella and E. coli negative.

7 If you would skip over the next slide,
8 please. Okay. There had been some publications
9 relative to bovine derived materials, and they are
10 used in the manufacture of regulated products. This
11 is more of a sourcing document. It's not really
12 giving you that good of an information on validation.
13 So we've spent a lot of time talking about validation
14 today, and just what is it that you want in
15 validation.

16 Do you want to go on to the next slide,
17 please. In CDER everything we look at is on a product
18 and process specific basis. There's not a general
19 category where, you know, there's one from column A
20 and one from column B. These are all rather well
21 reviewed.

22 If you take the principles of
23 sterilization and validation guideline or some of the
24 principles out of the ICH documents that address this
25 type of principle also, they have a lot of features in

1 common, and the first of these is that you need to
2 demonstrate the efficacy of the given procedure.
3 Whatever it is that you're doing to this product to
4 inactivate what its TSE load might be, I don't care
5 what it is, you still have to demonstrate that it's
6 efficient.

7 There should be a series of protocols.
8 They should be good, valid scientific experiments.
9 You need to demonstrate that you reproducibly deliver
10 a product free of the specified infectious agent.

11 These graded response experimental data
12 and control procedures should allow conclusions to be
13 drawn by the agency that you are showing us a valid
14 experimental approach to elimination of an agent.

15 These procedures -- next to the last
16 bullet. These procedures and conditions should be
17 fully representative and equal to your manufacturing
18 process. Don't show me something in validation
19 protocol that you don't do in your product. You won't
20 get away with that. Then all these protocols are
21 reviewed by microbiologists, not chemists, in the
22 Center.

23 Next slide, please.

24 Now we've had some various types of
25 products within the Center. I know we're still

1 addressing gelatin, but we want to take a look at
2 validation of the absence of the TSE agent in these
3 products.

4 The first thing that's helpful to remember
5 is you do this on a pilot or laboratory scale. We
6 would never ask you to add a SE agent to your
7 manufacturing premises. You should have a rather
8 consistent model system. Whichever animal, probably
9 rodent, that you want to use and whichever strain of
10 TSE agent that you want to use is perfectly
11 acceptable, as long as you have data that indicates to
12 us that you have a sufficient experience with these to
13 be able to predict their response and that your
14 inoculum is under control, that you have done enough
15 titrations with this inoculum so that it's within
16 limits and predictable.

17 You want this protocol to follow your
18 typical manufacturing procedure. Any step in there
19 that would have an effect on the agent, you want to
20 obtain samples and hit your animals at that step.
21 Follow all your manufacturing time frames.

22 You want to set up your design so that you
23 have a reproducible endpoint. You want to bracket
24 your LD50 for your inoculum. You want a good tight
25 control you that. You also want to bracket for your

1 inactivations. You want enough animals left there to
2 show -- You want to end up with a dilution's worth of
3 live animals, and you should have positive and
4 negative controls on everything.

5 The next slide. So we are still
6 maintaining an interest in the issue. We have some
7 regulatory framework, even though it's kind of a
8 zigzag approach to regulation for gelatin. We have a
9 number of protocols and can share information with you
10 on the type of information that you need to provide,
11 and we took a glance at a typical protocol, and I'm
12 stopping.

13 CHAIRMAN BROWN: Thank you, Dr. Vincent.

14 Here before we get questions, I should
15 poll the committee. Are you fatigued or can you take
16 the final presentation of the day now and hold your
17 questions for the previous three instead of two
18 patients -- two speakers. You'll notice, the laser
19 beam didn't go through my head -- or would you like a
20 break and have the final presentation and then a
21 discussion? I leave it up to the committee.

22 DR. TRAMONT: I vote to do the final
23 presentation.

24 CHAIRMAN BROWN: Now?

25 DR. TRAMONT: Now.

1 CHAIRMAN BROWN: Is there a consensus?
2 Would everyone agree to that? Very well, push ahead.
3 Dr. Schrieber.

4 Dr. Schrieber, in view of the committee's
5 indulgence, I would ask that you conclude not later
6 than 3:30. That's 35 minutes.

7 DR. SCHRIEBER: I will do my best. First
8 of all, I'd like to thank you for this invitation.
9 I'm a Senior Executive Director of DGF Stroess in
10 Germany, one of the leading manufacturers of gelatine
11 around the world, but here I'm representing the GME,
12 which is Gelatine Manufacturers Association of Europe.

13 This association consists of 12 companies
14 in Europe, Western Europe only. We have altogether 25
15 plants in Western Europe, running in nine different
16 countries. So this means, in reality, that the GME is
17 representing about 45 percent of the world production
18 of gelatin, all grades.

19 The only four companies not members of the
20 GME -- one bigger one, which is Agfa Gavaert in
21 Germany because they only manufacture photographic
22 gelatin, so they are not so very much really involved
23 in things we are talking about in the Association; and
24 three very small ones, two in Germany and the one in
25 Spain, which are not relevant for this audience here,

1 because they are so small that they don't export any
2 kilograms of their production.

3 About this presentation, I'd like to give
4 you here information about the background for the
5 different statements published by different official
6 bodies over the last years that the consumption of
7 gelatin is considered to present no significant risk.

8 As I'll explain in the next chart -- and
9 this might answer some of your questions from this
10 morning -- why European gelatin made from bovine raw
11 materials is a factor for the U.S. consumer. It will
12 show as well the actions we have taken over the years
13 to safeguard consumers' health with regard to the
14 consumption of gelatin, and it will address what I
15 think is the most important thing today, the different
16 safety components from raw materials through to
17 marketing, which all added together for the total
18 safety of all products.

19 So that's a split of gelatin manufactured
20 and consumed in different areas. When we look around
21 the world -- and this is only edible and
22 pharmaceutical gelatin, because I have skipped out
23 photograph or other technical applications which are
24 not a point of this discussion here today.

25 What you can see, about 24 percent of the

1 gelatin is made from pig skin. About 34 percent is
2 hide splits and 22 is made from bones.

3 When we look to the U.S. market,
4 consumption in the U.S. is coming close to what we
5 talked this morning, of course, but don't pinpoint me
6 on a percent exactly, because that's estimate: 55
7 percent in the U.S. is made from pig skin; 19 percent
8 is made from hide splits, and 26 is made from bone.
9 So this is consumption, not local production.

10 Where is this gelatin which is consumed
11 coming from? Again, altogether bovine edible,
12 pharmaceutical gelatin, because again I have skipped
13 out of this chart the pig skin, thus looking to the
14 bovine part of the whole cake.

15 So about 21 percent -- only 21 percent is
16 manufactured domestically. Thirty-nine percent of all
17 bovine comes from Western Europe, and about 40 percent
18 from the rest of the world, which is basically South
19 America.

20 Next slide, please.

21 Before I go into this, I'd like to address
22 -- to answer this question of tomorrow -- this
23 morning, excuse me. Are there any reasons why you are
24 going to use pig skin gelatin, bovine bone, bovine
25 hide? There are reasons behind it, much more reasons

1 than just talking about only economics or what is
2 available.

3 Of course, you remember this breakdown.
4 It's clear, when we have this kind of case, there is
5 no way to make all the gelatin just from pig skin or
6 just from bones or just from hide. This quantity of
7 single raw material would not be available at all
8 around the globe. This cannot happen.

9 When we look to, for example, why is a big
10 portion in the pharmaceutical industry based on bovine
11 sources, even the protein -- the gelatin protein is
12 very similar. There are some differences.

13 For example, capsules made from bovine,
14 either hide or its bone, will stay elastic. If you
15 would make the same capsules, soft gel, hard gel
16 capsules, just from pig skin gelatin, those capsules
17 would become brittle. Soft gel capsules could become
18 brittle like glass. It will fall down.

19 Therefore, there are really technical
20 reasons behind why mainly the pharmaceutical industry
21 is heavily dependent on bovine source gelatin. On the
22 other hand, one looks at the edible part, looking to
23 the Gummi Bear production, for this type of product
24 you need a very low viscosity type of gelatin to avoid
25 the -- by molding the Gummi Bears you will have tails.

1 You will have it all coming down on a string. So,
2 therefore, you need low viscosity gelatin. This means
3 you need pig skin gelatin, which is of low viscosity.

4 So you couldn't really put -- work very
5 good with bovine source gelatin.

6 Another example, gelatin in ice cream. In
7 an ice cream you have a mixture. You have gelatin and
8 other electrical charged hypochlorites, and then it is
9 very important which kind of isoelectric point your
10 gelatin has, and you have learned this morning there
11 are big differences in isoelectric points.

12 So, therefore, again it depends on your
13 composition. It's either that or that, what you have
14 to take. So there are many really technical reasons
15 for the application which are finally adding up, this
16 is the right or this is the wrong gelatin I have to
17 use for my specific product.

18 Next shot.

19 So when we look to the safety for gelatin,
20 there are basically five points which are coming
21 together. That's why I've used the title: The
22 territorial, which is sourcing; the source of raw
23 materials which is the type of raw materials; removal
24 and/or inactivation done by the production process;
25 then, of course, the route of administration, because

1 you are talking mainly about the oral route which is
2 a very low risk; and then, of course, the quantity of
3 product to consume, and we have heard many things
4 about this this morning.

5 I think that our industry has really taken
6 very early and very serious approach to this product.
7 When it became known that BSE is epidemic in the U.K.,
8 we immediately looked into the situation, what is
9 available from the literature about a process, about
10 the chemicals we are using, and we found out basically
11 really talking about lime or hydrochloric acid,
12 nothing is published. Nothing has been studied, and
13 no one has the intention to do something from, let's
14 say, official bodies.

15 So what we did in Europe, we went straight
16 away to Brussels and asked the European Commission to
17 sponsor a study of our process, but the reply was
18 totally negative, because they told us, look, we are
19 very short on money; gelatin is considered to be safe;
20 we can't sponsor such a study. We have more important
21 cases we have to look into. So, nothing.

22 So, therefore, we decided we have to add
23 comfort to the safety of our product. We have to add
24 data to the data base available. So if there is no
25 other way. We are going just our own way. We are

1 doing our own study. So we decided already in '92 to
2 carry out validation studies and two very specific
3 inactivation steps where we thought these are the most
4 important ones.

5 Then, of course, in May '94, we have been
6 here altogether, GMIA and ourselves, to make a safety
7 assessment presented to the FDA. Then the same year
8 we had to do the same thing in Germany to the German
9 BGA with regard to the safety of pharmaceutical
10 gelatin.

11 As you might know, they have this famous
12 20 point system to add up the inactivation and so on.
13 Then, of course, we looked into this question from
14 this morning. What about the potential for
15 contamination by CNS of our bones? Was that okay? We
16 have to look very deep into this thing.

17 So we designed a study of the removal of
18 CNS tissue by our degreasing process of fresh bone.
19 So this was carried out by the University of
20 Goettingen. I will tell you something later about
21 this.

22 Then we continued, of course, our
23 consultations with the FDA in April and May last year.
24 We provided the new available additional data as well
25 coming out of this study. We gave the new protocol of

1 the Inveresk study to the FDA. We continued. In
2 February of this year we made a presentation about the
3 safety of our product at the EMEA in London, and just
4 recently in March we made a presentation of the latest
5 available data, and you will see this later on,
6 Inveresk at the WHO scientific consultation in Geneva.

7 I think this is quite important. So what
8 more -- After this consultation, what did the working
9 group of the WHO state? The raw material used for the
10 production of gelatin should be sourced from safe
11 materials. Could be either safe countries, safe raw
12 material. So at least low risk -- let's put it this
13 way.

14 In addition, manufacturing process
15 utilizing production conditions which have been
16 demonstrating to significantly remove or inactivate
17 TSE infectivity in soft tissues should be used. If
18 this is done, gelatin is considered safe for all
19 purposes.

20 So this was the statement, conclusion of
21 this group of the scientific world, as our Chairman
22 has been at this meeting. Next slide, please.

23 What are these three basic safety
24 components? Low risk countries, materials without
25 infectivity, and removal and/or inactivation done by

1 the process.

2 So let's go to the first one. This, I
3 feel, is a very important thing. Raw materials of
4 British origin is not used. So, therefore, we are out
5 of countries where BSE really is epidemic. In all
6 other countries, the risk is extremely low or
7 nonexistent. We have heard about this.

8 The bones and skins we are collecting from
9 the meat industry are, of course, controlled by the
10 official veterinarian services. They come only from
11 animals which have been inspected under a post mortem,
12 and they are recognized as fit for human consumption.
13 So we are basically using the bones the housewife
14 could take home from the butcher shop to make their
15 bouillon.

16 Next slide.

17 Now let's talk about the type of raw
18 materials we are using, the nature of the tissue.
19 They are using tissue without infectivity or without
20 detectable infectivity, I have to say. The pure bones
21 and skins, as are milk and meat -- they are the same
22 kind of material -- are classified without detectable
23 infectivity. That's the pure stuff.

24 Only bones might have some extraneous
25 materials on the surface, and you can't really totally

1 exclude it, but this is removed by degreasing, and we
2 will come to this and look into the Goettinger study
3 we saw.

4 Even when we get the material into the
5 real gelatin process, there is already some
6 pretreatment done. In the slaughterhouse, and they
7 talked about this this morning, separation of
8 potentially infected material in France and
9 Switzerland by regulation. It's the law. Brains,
10 spinal cord, they have to take out, incinerate.

11 Then we have the degreasing plant. That's
12 some kind of a pretreatment, and there is a difference
13 here in Europe and in United States, because in Europe
14 the degreasing is done by the gelatin industry itself.
15 Here in the United States, the degreasing is done by
16 the meat packer. So there is a difference, and the
17 process is a little bit different. So there are some
18 differences.

19 In the degreasing plant, of course, we can
20 inspect the incoming raw material and, if you would
21 see a full head, of course, we sort it out. It should
22 not be, but it could happen, and then we can pick it.

23 Degreasing bones with hot water, you have
24 heard here, it's done in its own step. We are using
25 hot water. In the tannery, remember, the hide split

1 is the tender part of the hide. So there's a
2 pretreatment in the tannery. It's pre-limed,
3 dehaired, and then it's split. So the outer part, the
4 hairy side, becomes leather, because it's tanned. The
5 meat side is basically waste, and the center part --
6 this is the so called hide split. That's our raw
7 material. It's like the meat in the burger. That's
8 what we are using.

9 Now we are coming to the process. What
10 really is the process with regard to adding safety to
11 our product? So we went into evaluation of gelatin
12 processing and looked at what is the best way to
13 validate, and there are some experimental constraints.

14 First of all, no test of infective study
15 material for production trials would be available,
16 because we have heard there's no testing, and no one
17 would really take a risk if we would collect -- let's
18 put it in this way. If you would go to U.K., if you
19 would pick bones from clinical infected animals to run
20 a trial in the plant, who could take the
21 responsibility to do such kind of experiment? I
22 wouldn't do it.

23 So, therefore, there is no way to make a
24 complete trial in the production side. So we have to
25 go in many things to the laboratory scale. Bones

1 cannot be inoculated and tested directly, another
2 problem, because we can't inject -- Even ground bones
3 you can't inject into a mouse brain. No way.

4 The pilot plant, if you would scale down
5 the process, we have many education processes which
6 are very important for washing and purification. You
7 can't really duplicate this when you scale down the
8 process from a big tank of, let's say, 40 cubic meters
9 content to 100 milliliters. This wouldn't work.

10 Then due to the fact that the potential
11 infectivity is very low, you can't measure it. So,
12 therefore, we need an artificial overlook for this
13 kind of measurement to see something, to calculate
14 something.

15 Next slide.

16 So what really do we decide? We have to
17 look into the degreasing process to verify to what
18 extent we are able to get rid of any surface material
19 of CNS in degreasing.

20 We looked into the acid treatment to see
21 what effect that this is, because what I said, no
22 literature data are available for hydrochloric acid;
23 and we looked into liming.

24 Basically, you can say -- The question
25 came out this morning. Gelatin manufacturing is very

1 standardized throughout the world. So in Europe the
2 process is the same what you have seen here this
3 morning.

4 The reason for this is that there are --
5 Chemically, there are limits what you can do. You
6 have some limits with regard to the acid treatment.
7 If you would go too long, the concentration of the
8 acid would be higher than what we are doing. Then we
9 are losing yield. So the protein would become
10 soluble.

11 The same is going to happen with the
12 alkaline. The maximum we have seen today might be up
13 to 70-80 days. If you would go for 120 days, you
14 would have your yield in the effluent plant and not
15 any longer to make gelatin.

16 With regard to this, that's fine. The
17 result is that the variations you have within our
18 industry are very, very small, and this is one of the
19 reasons why I can speak here on behalf of the European
20 gelatin industry and not just on behalf of one
21 company, because basically the process we are using is
22 quite the same.

23 What we did not test on our own is
24 sterilization, because there are sufficient literature
25 data available for this type of process.

1 So what did we do? We said, okay, bone
2 degreasing -- you see what's going to happen with CNS
3 tissue. This could really be done in an industrial
4 test, because there is no risk. Germany -- we did
5 this in Germany. It's a non-BSE country. So no risk
6 to our workers, easily to be done, even with overload.
7 We come to this.

8 I think demineralization is okay. We have
9 to go in a lab test. Liming has to be done in a lab
10 test. For the sterilization we basically used the
11 number from books.

12 Next slide, please.

13 So that's the result of the degreasing
14 study carried out in an industrial level. But first
15 of all, what we did -- and we used marker proteins.
16 Mainly, these two are very specific for CNS, and the
17 tests have been done with immunoblot and ELISA tests.
18 So these are very, very sensitive tests, very
19 specific.

20 First, we looked into our standard process
21 on our standard bones. Do we find anything? And
22 these numbers are all published. That's in the
23 literature. You can read it there.

24 The first round, we went into our normal
25 production, and we looked into dozens of samples. In

1 none of them after degreasing we found anything.
2 Okay. You could say, okay, by good luck no one,
3 there was an input. So therefore, there is no output.
4 So this is not really good proof that the process
5 works.

6 So we finally decided we have to run an
7 artificial test, an experiment, and we decided to run
8 an industrial scale on about 20 metric tons of
9 material we have been running heads through with
10 brain.

11 We bought them separately. We ran it
12 through the whole process, and here we have been able
13 really to find numbers and to check numbers. What was
14 the result? The removal rate of this specific
15 proteins, these marker proteins for CNS, was between
16 98 and close to 110.

17 So this means that the degreasing process,
18 due to the education, the time, the hot water, is very
19 effective to remove CNS which is, incidentally, on the
20 surface, because it can't be anywhere else. So this
21 time of contamination takes place only on the surface.
22 So, therefore, it's relatively easy to remove it.

23 Next slide, please.

24 So the next -- So this was the first step.
25 The next step, what we did was the inactivation study

1 done by the Inveresk Research Institute, and that will
2 give you a short overlook what has been done.

3 Inveresk used for this study, this well
4 known scrapie brain strain ME7, which is very high
5 infective. They are using special adapted mice which
6 are very responsible, and will give you very early
7 response with regard to the disease.

8 It is a standardized test, and they use,
9 I think, around the world. So this study material is
10 breeding in mice, and then the infective brain from
11 these mice have been prepared, and then used for the
12 experiment, which, of course, has nothing to do with
13 the real reality of making gelatin, just running
14 experiment to see what our process does.

15 So we split into the infected brain
16 tissue, treated part of it according to our production
17 conditions with saturated lime. Another sample was
18 treated, of course, with acid, again according to
19 demineralization conditions. Then we had the positive
20 control and the negative control and, of course, to
21 have countable numbers you need all this many -- of
22 course, you don't know really how many beforehand --
23 dilution steps to scale down by dilution to have
24 surviving mice.

25 So this was the experiment, and then to

1 check here -- again, the standard -- you're looking at
2 survival in dead animals, a clinical -- It was a
3 clinical type of scrapie after nine months. After 18
4 months, of course, all brain are investigated directly
5 on the brain slices on the microscope.

6 Next slide.

7 So what was the outcome of this Inveresk
8 study? So these are the results, the interim results,
9 of the nine months, and this is only the percentage of
10 mice which died. Here you see as well the dilution
11 steps which have been used for the positive control,
12 for the acid treatment, and the lime treatment.

13 You can easily see, for example, here
14 between acid and positive control at the dilution of
15 10^{-3} 50 percent died. For the positive control you
16 had to go down to 10^{-6} to have the same number. It
17 was even better, like expected, with lime, because it
18 was clear from the scientific knowledge that the
19 alkaline will give you more effect than the acid.

20 Well, then after 18 months when we looked
21 into the final results, there was a great
22 disappointment for us, because due that we stopped
23 dilution here and there, we had not gone far enough
24 down to have survivors. Only one survived here.

25 You can see from the trends, if you look

1 to this trend, most probably we would have needed one
2 more dilution step to have survivors here and
3 survivors there. But okay, this dilution step was not
4 done, because the point was that the starting
5 infectivity from the brain was higher than expected
6 and calculated. So this was a mistake of the
7 protocol.

8 If we would have known that we have been
9 starting that high, we'd have used another step. So,
10 therefore, of course, we have seen there is something
11 going to happen, and the trend is there, but we don't
12 have really very good results. So we have to start
13 another study, a second one.

14 You can see here, these are the new
15 dilution steps of the second one, though we are going
16 further down in dilution to give us a guaranty that we
17 will have survivors where we can count on to have
18 real numbers, countable numbers. We said, wait, there
19 is an effect, but is it 2 log, 3 log? I think the
20 difference will be within plus/minus 1 log for that
21 specific thing.

22 When you look from here to here, the
23 difference between nine months and 18 months is
24 basically plain, within 1 log. 10^{-6} we have a
25 difference. Here, the same result. Here, roughly the

1 same result. So there is normally not a big
2 difference, but most of the mice are dying within the
3 first nine months, but we always have some late dying
4 animals and -- okay, this happens.

5 So where are we at the moment? And why is
6 the reason? Just to verify what is the reason behind
7 the idea, we started to come up to the 8.2 just with
8 the two samples, and then we take the clearance
9 factors out to nine months. That's a reduction of
10 infectivity. After this treatment, remaining
11 infectivity was $10^{5.9}$, $10^{4.4}$.

12 Then we used the maximum dilution, 10^3 and
13 10^2 , which means after taking into consideration these
14 numbers are the correct numbers, and the final would
15 have been the final number. After treatment and
16 dilution, the remaining infectivity was still $10^{2.9}$ and
17 $10^{2.4}$, which is too high to have surviving mice after
18 18 months. Everyone who has run this type of
19 experiment knows this. Okay.

20 So we started a second study, and interim
21 result of this second study are already presented
22 recently at the WHO consultation meeting in March.
23 Again, it's only nine months, because this study will
24 run until spring next year. So it's not final.
25 Therefore, the numbers, of course, will change a

1 little bit, as usual.

2 I'm just going to use one or two slides
3 from his presentation. Just one more about the time
4 frame. So this is about the first study. So this
5 ongoing study commenced March '96, anticipated
6 completion in February '98. So the results are per
7 3rd February of this year.

8 Okay. Now I can go, of course, through
9 all this time of slides, but I think this doesn't help
10 you a lot, because it might even confuse you, but just
11 going to this type of -- So he told where we are with
12 each dilution step, how many mice are inoculated, what
13 are the number of surviving, how many are dead
14 already, just to give you an overview which will help
15 you more, I think, and to save some time.

16 Again, like in the first one, percentage
17 of dead mice -- Again, you have the nine-month acid
18 positive control. You can see dilution 10^{-2} , 50
19 percent dead, 50 percent alive. Here, all 100 percent
20 are still alive.

21 In the positive control here are already
22 78 percent are dead, 11 percent are dead, and then,
23 okay, it starts here as well with 100 percent
24 survivors; and even again, it's like a copy from the
25 first one. With liming, this time we even looked into

1 the time frame of liming, whether more days, 20 days,
2 45 days, 60 days, give you more effect or not. It
3 doesn't look like.

4 The numbers again was in one order of
5 magnitude within 1 log. We have some differences, but
6 this is, I think, not very significant. Here they are
7 all still the same, but again there's a big difference
8 form here to here, even with three, four times -- 4
9 log more dilution. We are already at the 89, 80
10 percent, dead mice.

11 Again, this clearly shows that this
12 treatment has an effect. It again shows that alkali
13 gives us more than acid, but whether it will stay
14 exactly what it is or whether it comes a little bit
15 closer, okay, I don't know. We will see this in
16 spring.

17 This means we have a clear tendency, even
18 though we have no results, because we have to wait
19 eighteen months.

20 What are the conclusions from the Inveresk
21 study? Up to nine months, basically, we can say that
22 the acid treatment reduces infectivity to being ten
23 and 100-fold. That's somewhere in this ballpark.
24 Could be 150. Could be 80, but this doesn't change
25 anything.

1 Alkaline reduces infectivity between 1,000
2 and 10,000-fold. That's a number we are in somewhere
3 between.

4 Then, of course, we heard just before my
5 speech from Bob. Of course, sterilization can play a
6 very important role. Many studies have been published
7 about the heat treatment, and when we looked into our
8 conditions and what have been published, we can say at
9 least that's a worse case.

10 Accidental remaining infectivity after all
11 the other treatment will be reduced by a factor
12 between 100 and 1,000. I think that this is very
13 conservative, but we are talking about worse cases and
14 not glorify the situation.

15 What else do we have? What else do we
16 have in our process with regard to potential of
17 inactivation? We have heard about the ion exchange.
18 So this can reduce, and this is the standard process
19 in our industry. It's implemented. You have seen
20 this this morning.

21 You have heard about oxidizing agents.
22 Sodium hydrochloride might be a problem for us, but
23 for example, hydrogen peroxide is widely used in our
24 industry; but of course, this has been validated
25 individually, because the percentage, the timing might

1 be different. So this would mean really something to
2 be done, company by company.

3 The same thing, washing titration. We
4 have 20-25 washing steps in the process. Again we are
5 talking about surface contamination. We are using up
6 to 60 liters of water per kilogram of bone chips. We
7 have all the titration steps. So all those things
8 will have some purification effect -- of course, not
9 validated yet, but we have not to forget about it.

10 So this means then we look to the safety
11 assessment. Again about the three basic facts: No
12 raw material from the U.K. is used. The potential for
13 exposure to CNS is very low. If there is something,
14 it's washed away, at least 99 percent. The
15 manufacturing process removes and inactivates
16 infectivity.

17 So what is the final conclusion? From our
18 point of view, there is no significant potential for
19 transmission of TSE to humans by consumption of bovine
20 gelatin made in Europe.

21 Thank you for your patience.

22 CHAIRMAN BROWN: Thank you very much, Dr.
23 Schrieber.

24 Well, we welcome questions from any of
25 the committee members for any of the three previous

1 speakers, Dr. Rohwer, Dr. Vincent, and Dr. Schrieber.
2 Ray?

3 DR. ROOS: Yes. Bob, maybe you would be
4 the best one to answer this. There are clearly some
5 unusual properties of the BSE agent, and I'm wondering
6 whether those extend into resistance to some of the
7 physical agents and sterilization conditions you
8 mentioned.

9 So do we know anything specifically? Do
10 we have data similar to what you described, I guess,
11 for the scrapie agent with respect to BSE?

12 DR. ROHWER: Well, it's an excellent
13 question, and there's a lot of concern about the
14 relevance of mouse and hamster adapted scrapie to both
15 BSE and CJD.

16 There's very limited data to provide any
17 direct assurance. In answer to your question,
18 comparing mouse and hamster scrapie and mouse and
19 mouse adapted CJD, the spectrum looks very consistent,
20 and it appears that there isn't a lot of variability
21 there, but in terms of BSE itself, there's so many
22 unique features of that agent that it is a cause for
23 concern.

24 I know that David Taylor has some
25 experiments in progress at the MPU looking at the

1 inactivation of the BSE agent. On the other hand, I
2 also know that the way he's designed those, he's again
3 looking at worse case situations. So he's going to
4 find -- I think you can predict that he's going to
5 find that, if you put a brain macerate in a tube and
6 put it in the autoclave, he's going to have a lot of
7 survival.

8 I would rather see those experiments done
9 in a kinetic fashion where you could actually compare
10 rates of inactivation from these things, and see if
11 there are any intrinsic differences between the
12 agents. That type of data just doesn't exist.

13 CHAIRMAN BROWN: Does Taylor also not have
14 in his rendering validation experiments some data on
15 both scrapie and BSE? He surely must have data on
16 BSE.

17 DR. DETWILER: Yes.

18 DR. ROHWER: Right. The problem with
19 interpreting those experiments, of course, is that
20 they are cross-species experiments. So the
21 sensitivity is rather low. In the rendering
22 experiments that were done, they only had three logs
23 or possibly even less infectivity, to begin with; but
24 to the extent that you can interpret them, they do
25 seem to be susceptible to similar types of insults --

1 to have similar sensitivity to these things.

2 The experiments he's doing right now, I
3 think, will be much better, but again even those are
4 subject to this same question: Is mouse adapted --
5 These are going to be done with mouse adapted BSE. Is
6 mouse adapted BSE relevant to the bovine strain?

7 As soon as you move this stuff into
8 laboratory models, that's always going to be a
9 question. My own feeling is that the only way to
10 resolve these issues is to look at the experiment in
11 a number of different host/strain combinations and
12 hope that the answers all converge on one answer, and
13 then that will provide a lot of confidence for
14 extrapolating it to the less accessible system that
15 you're really interested in, BSE in cows or CJD in
16 humans.

17 CHAIRMAN BROWN: Yes. Linda?

18 DR. DETWILER: I have a question for Dr.
19 Rohwer.

20 In your paper, in David Taylor's paper in
21 1994, and in Paul's, what's the species of origin for
22 each of those, and what was the strain of scrapie? If
23 you were giving -- second part -- a worse case
24 scenario to use, that you would use -- To try and test
25 a worse case scenario, what strain of scrapie would

1 you use?

2 DR. ROHWER: We used the -- The strain
3 that I used was the hamster 263K strain, which in some
4 sense is a worse case strain, because it has the
5 highest titers. So we can actually challenge the
6 system with almost two orders of magnitude more
7 infectivity than you can in a mouse adapted strain.

8 The experiments that our Chairman did were
9 also done with that strain. The experiments that
10 Taylor has done were done with mouse strains. He used
11 the 139A strain, and he has also used the 22A strain.

12 There is also a suggestion in the
13 literature that the 22A strain, which is a sheep
14 scrapie adapted mouse strain, is more resistant than
15 the sheep scrapie adapted mouse strain 139A. There
16 are multiple strains of mouse adapted field scrapie,
17 and they differ somewhat in their presentations
18 clinically, their incubation times in various animals,
19 and they may differ somewhat in their resistance to
20 these physical inactivations.

21 The problem with interpreting that data is
22 that there are other experiments that show that they
23 are not so different. So again, because these
24 experiments are so hard to do and they're so
25 expensive, we don't have the luxury that Carol Vincent

1 was mentioning very often of replicates.

2 It's often done once, and you're happy to
3 have been able to do that. If it's done again, it's
4 done in a slightly different way, and so you're trying
5 to compare McIntosh apples to Jonathan apples in many
6 of these cases. You know, they're not exactly
7 equivalent.

8 If this was polio, we could set up three
9 parallel experiments, do them all the same time or do
10 them on three different weeks, and you would have the
11 answer, and you have a lot more confidence in the
12 answer; but that's one of the aspects of this field,
13 that one of the reasons why there's this big question
14 mark -- you know, we don't know enough about it.

15 CHAIRMAN BROWN: But also, you know, lest
16 we get overwhelmed by this detailed discussions of
17 strain differences, they exist for certain. In some
18 cases they can be reasonably important. In other
19 cases, they can be trivial, but it, I think, is most
20 important to understand that there are far more
21 similarities than differences amongst these strains.

22 They are awfully much closer together than
23 they are to polio or herpes virus. So I think we
24 should not turn up our noses just because a strain is
25 being used, with the caveat that they may not be quite

1 the same.

2 Yes, Dr. Wolfe?

3 DR. WOLFE: I would just like to ask Carol
4 Vincent: Having seen -- Maybe you saw it before --
5 Mr. Schrieber's presentation, how does this fit in
6 with your notion, as you presented it, of what FDA or
7 CDER requires in terms of process validation?

8 MS. VINCENT: You're asking if the second
9 study looks better?

10 DR. WOLFE: Well, anything that you saw,
11 the second study --

12 MS. VINCENT: I couldn't see the slides
13 too well from where I was, but there are more
14 dilutions there. It does appear to have a broader
15 range, and I'm looking forward to seeing the data when
16 it's finished.

17 DR. WOLFE: As I mentioned this morning,
18 we were talking about studies where you've got in each
19 group nine animals or something like that. So even
20 when you get down to the zero infectivity, you've got
21 a confidence interval that still would be compatible
22 with some infectivity.

23 So how does that play into your
24 considerations?

25 MS. VINCENT: Well, doing these titrations

1 in groups of nine or in groups of ten animals, I mean
2 it's been a standard way to test animal viruses for at
3 least 50 years. I'm sure somebody in this room could
4 give me the correct figure on that, but in groups of
5 ten in a tenfold dilution or fivefold dilution or
6 twofold dilution, whatever makes your system work, is
7 okay.

8 Bob, I wasn't actually saying to do the
9 entire validation a number of times. I was talking
10 about just the control titration, but this is the way
11 things have been done for a very long time, and
12 there's a lot of experience with that system.

13 DR. WOLFE: Yes, I just think this agent
14 is much worse than most anything we've ever seen
15 before. So the extra caution may make some sense
16 here in terms of the numbers and so forth.

17 MS. VINCENT: I couldn't address that
18 statistically, but the groups of ten don't bother me.

19 CHAIRMAN BROWN: Dr. Schrieber, two
20 questions. What is the pH in your lime slurry in this
21 particular experiment?

22 DR. SCHRIEBER: 12.5.

23 CHAIRMAN BROWN: But the pH of the actual
24 mixture?

25 DR. SCHRIEBER: Yes.

1 CHAIRMAN BROWN: That is the pH of the
2 actual specimen, not what you put into it, but the
3 actual specimen?

4 DR. SCHRIEBER: No, it's oversaturated.
5 So it stays all the time at 12.5.

6 CHAIRMAN BROWN: Well, we did experiments
7 in which we used 1 normal sodium hydroxide as an
8 additive or we added sufficient sodium hydroxide so
9 that in water the sodium hydroxide would have had a pH
10 of 13, but in point of fact, with the tissue mixed in,
11 the pH dropped a half-log. So it was not 13. It was
12 12.5.

13 DR. SCHRIEBER: No, it's tested 12.5.

14 CHAIRMAN BROWN: The actual specimen that
15 you were using?

16 DR. SCHRIEBER: Yes.

17 CHAIRMAN BROWN: Okay. The second is: In
18 view of this absence of bracketing in the first
19 experiment, why the devil didn't you just go up zero
20 to ten for all of them? It's not that much more work
21 to put on extra cages so that you would know that you
22 wouldn't miss your endpoints.

23 DR. SCHRIEBER: Okay. This protocol was
24 even reviewed before by Dr. Timberland, and he found
25 it in order, because it was thought that the study

1 infectivity would only be maximum 10 up to the 7.3 or
2 so. So, therefore, when the calculation was made and
3 -- Of course, it has been expected as well that we
4 might have anyhow one log more inactivation than what
5 we see in the moment. So it would have been
6 sufficient.

7 CHAIRMAN BROWN: Well, I agree that, you
8 know, the first experiment -- that was a legitimate
9 thing to expect, but having had that result, I'm a
10 little surprised you didn't give yourself a little
11 more leeway and avoid the possibility even of not
12 getting a final bracket on your second experiment.

13 DR. SCHRIEBER: But I think we are
14 followed now with a dilution --

15 CHAIRMAN BROWN: Yes, but you're still at
16 nine months, and you saw what happened between nine
17 and 18 months the first time around.

18 DR. SCHRIEBER: But we have still a
19 security level in the moment in dilution of more than
20 four logs.

21 CHAIRMAN BROWN: I hope whoever designed
22 it made an accurate and shrewd guess, but I think you
23 still have the possibility of running out of brackets.

24 DR. O'ROURKE: Mr. Chairman, they also
25 started with considerably lower titer. You'll notice

1 his curve is adjusted down by maybe three or four
2 logs.

3 I'm sorry. The initial inoculum on your
4 second trial is considerably lower in titer at nine
5 months than the inoculum on your first trial.

6 DR. SCHRIEBER: Yes, but infectivity for
7 the first trial was as well somewhat lower than at the
8 end. Of course, it went up somewhat, because I think
9 after nine months in the first experiment we have been
10 at 7.3 and ended up at 8.2. In the moment we are at
11 6.7, I think, with the lime.

12 So it will go up further on. That's for
13 sure.

14 CHAIRMAN BROWN: Yes?

15 DR. ROOS: Just since you're up there, I
16 had a question about it. I guess I had two concerns.
17 One is we're clearly not exactly dealing with BSE.
18 We're dealing with scrapie, but this is interesting
19 data.

20 The other had to do with how well we could
21 extrapolate the sensitivity of this agent to lime and
22 acid with respect to what you're doing with gelatin,
23 and the fact that these are bone chips, I guess, when
24 they were exposed to the lime and the acid, or am I
25 wrong?

1 DR. SCHRIEBER: No.

2 DR. ROOS: Do you think this is -- to both
3 homogenates -- Well, this is brain homogenate, and the
4 accessibility of this lime to acid in the case of your
5 gelatin preparation, how much can we extrapolate this
6 data to that?

7 DR. SCHRIEBER: I think still it would be
8 exactly the same, because what I said before, just in
9 case CNS is on the surface of the materials or it's
10 either in excess, and after this many days of liming,
11 alkaline is everywhere. So we need about two, three
12 days diffusion to get to the center, for example, of
13 the bones.

14 We know after three days really alkaline
15 is in the center of the bone pieces, because as you
16 have learned this morning, these bones are grinded.
17 So they have the size of a fingernail. So it's not
18 big pieces. So about latest after three days alkaline
19 is in the center, and then it would stay.

20 CHAIRMAN BROWN: Question?

21 DR. WHITE: Well, I guess the way I'm
22 looking at what you're presenting, it clearly is not
23 a model for what is being done to make gelatin, but
24 the message that I'm getting -- and I just want to
25 hear if that is a correct message -- is that there are

1 conditions under which a transmissible spongiform
2 encephalopathy agent can get through this processing,
3 whether it's alkaline or whether it's acid.

4 It may not be a combination of agents, but
5 it does look like, when you use certain titers of
6 viruses or certain dilutions of infected brain, that
7 you do not get full inactivation of the agent.

8 DR. SCHRIEBER: If the starting titer
9 would be extremely high, then you are right, but where
10 should the starting titer come from?

11 DR. WHITE: I agree. I don't think that
12 what you're doing is equivalent to what is being done
13 to make gelatin, but clearly, if you did have a high
14 concentration of virus, it can get through those
15 individual processing steps.

16 DR. SCHRIEBER: We have significant
17 reduction in titer, but you are absolutely right. If
18 you would -- which is not possible, but if you would
19 try to make gelatin just by using brain, straight 100
20 percent brain, and this brain would be really highly
21 effective, I think there would be remaining
22 infectivity, but that's not what you are doing in
23 reality.

24 CHAIRMAN BROWN: Question? Yes?

25 DR. HOEL: I had one. In chemical

1 toxicity, you always run mice 24 months. I was just
2 curious why you stopped -- these experiments are all
3 stopped at 18.

4 DR. SCHRIEBER: Excuse me. I'm not this
5 expert in this kind of experiment.

6 CHAIRMAN BROWN: We can answer that for
7 you.

8 DR. SCHRIEBER: Thank you.

9 CHAIRMAN BROWN: Mice in cages tend not to
10 live much more than 24 months. So you're approaching
11 the end of their unnatural lifespan, and at that point
12 a lot of them are dying from peculiar -- well, old age
13 or other diseases. Also, as you keep a mouse longer
14 and longer in cages, you run the risk of getting
15 deaths from intercurrent illness.

16 So on that end of it, you're looking at
17 background noise that increases substantially towards
18 the last few months of a mouse's life.

19 Second, by and large, you've got 99
20 percent of any deaths from scrapie that will occur
21 within 18 months. So that the last six months
22 fundamentally simply increase the noise without
23 increasing the sensitivity.

24 DR. HOEL: Okay. So, basically, what
25 you're saying is that it's like an early occurring

1 tumor compared to typical tumors for carcinogenesis
2 studies. You don't see much at 18 months typically.

3 CHAIRMAN BROWN: That's right, and between
4 18 and 24 you see practically nothing in terms of
5 additional scrapie illnesses.

6 MS. HARRELL: One question for Mr.
7 Schrieber. I would like to know, when was the use of
8 British raw materials for gelatin halted? I mean, the
9 raw materials for gelatin production halted.

10 Number two, when was it -- or what was
11 done with the British raw materials and the gelatin
12 produced before the ban?

13 DR. SCHRIEBER: Okay. Of course, before
14 we stopped it, it was used to manufacture gelatin.

15 MS. HARRELL: When was it stopped?

16 DR. SCHRIEBER: The first step was to stop
17 it for the use of making pharmaceutical gelatins.
18 This took place in early '94, and completely we
19 stopped it early last year, by the end of March when
20 we have heard about this new cases of CJD. We still
21 believed that even gelatin made in U.K. of British raw
22 material is still safe, but okay, we have to stop it
23 to have really the lowest possible risk.

24 MS. HARRELL: The second part was what was
25 done with the raw materials and the gelatin produced

1 from those raw materials that were produced prior to
2 that?

3 DR. SCHRIEBER: Okay. I can answer this
4 for our own operation only. In the moment we have as
5 well one plant in the U.K. So all this stock and
6 inventory we have had at this time manufactured before
7 has been sold in the meantime as glue.

8 CHAIRMAN BROWN: Are there other questions
9 from the committee? Yes, Ken? I mean Will.

10 DR. HUESTON: May I pursue this? I
11 certainly agree that sourcing is the primary
12 prevention step in this whole process. If I might
13 just make sure that I understand some of the sourcing
14 issues.

15 Your sourcing or the gelatin manufacturers
16 of Europe were sourcing throughout Europe raw
17 material. Is that correct?

18 DR. SCHRIEBER: Yes.

19 DR. HUESTON: All right. Also, so the
20 sourcing and your contention that the source material
21 is low risk is based on the concept that there is a
22 surveillance system in place throughout Europe?

23 DR. SCHRIEBER: Yes.

24 DR. HUESTON: And yet if I look for data
25 about surveillance systems, I am only able to find

1 substantiation of active surveillance systems in a
2 handful of European countries. In fact, a number of
3 European countries have no data available about
4 examining cattle brains and no information available
5 about a surveillance system.

6 DR. SCHRIEBER: I think there is a
7 guideline from the OIE how the system has to work in
8 Europe, and I assume -- excuse me. The only thing I
9 can say, I assume that the different countries, that
10 the regulatory bodies in the different countries have
11 the right systems in place.

12 Sorry. I am not out of the meat industry,
13 but I think is the general understanding in western
14 Europe, that we have to be very careful, and all the
15 things have to be followed very closely; and as far as
16 I know, the OIE will very soon implement a thing and
17 even improve the system for surveillance.

18 DR. HUESTON: But the OIE, of course, is
19 a standards organization, and does no surveys of
20 compliance. I guess, are you aware of any surveys of
21 the level of compliance with the European countries
22 from which your manufacturers are sourcing material?

23 DR. SCHRIEBER: I don't have this answer.
24 Sorry.

25 DR. HUESTON: So for instance, the British

1 are now putting out a monthly enforcement bulletin
2 that lists in quite some detail the compliance. Are
3 you -- I'm not aware. I just wonder, are you aware of
4 any other country that has a similar level of --

5 DR. SCHRIEBER: No. I've never seen a
6 similar document from any other country. I think this
7 is all kept within the regulatory bodies, though
8 nothing is published.

9 DR. HUESTON: Then for your -- I mean, I
10 respect the assumption, and we all hope that it is, in
11 fact, in place. Do the gelatin manufacturers of
12 Europe then have a quality control program or do you
13 have your own assurance program that you are sampling
14 or investigating the sources of your raw materials to
15 assure that --

16 DR. SCHRIEBER: We are auditing our main
17 suppliers of raw materials, yes.

18 DR. HUESTON: You are auditing?

19 DR. SCHRIEBER: Yes.

20 DR. HUESTON: All right. Good. You also
21 mentioned that at the moment only Switzerland and
22 France has specified bovine material regulations in
23 place, and --

24 DR. SCHRIEBER: Plus U.K.

25 DR. HUESTON: Plus the U.K., of course,

1 right -- which means that, of course, Portugal and the
2 Netherlands and Ireland, all of which have reported
3 BSE in native animals, are not -- do not have
4 specified material --

5 DR. SCHRIEBER: I think that this question
6 is not of a big concern to us. For example, where do
7 we have degreasing plants, and we have a certain limit
8 with regard to transport fresh bones to a degreasing
9 operation. So where are they located? They are in
10 Germany. They are in Belgium. They are in the
11 Netherlands, and they are in France. Basically,
12 that's it.

13 So no one would bring fresh bones from
14 Ireland to degrease it somewhere else, because this
15 would be too expensive to complicate by, but I imagine
16 all Irish bones will stay in Ireland.

17 DR. HUESTON: Right. But spinal columns
18 as an example of cattle across Europe are entering the
19 degreasing process?

20 DR. SCHRIEBER: If there is trade in
21 carcasses, which could, of course, take place, and
22 that's nothing one could exclude, it could happen.
23 Yes, you are right.

24 DR. HUESTON: You mentioned that the
25 occasional head that shows up at the degreasing plant

1 is manually removed.

2 DR. SCHRIEBER: Yes. We have sorting
3 belts with all the bones running through. We have
4 persons controlling, because sometimes you find a tin
5 of Coke or something like this. You have to put all
6 this stuff, and they're putting out -- If a head shows
7 up, they put it out, because there's another reason
8 for this as well. We don't like horn in our raw
9 material, mainly for photographic purposes. So we are
10 very keen even before to have no heads in our process.

11 DR. HUESTON: That's a good thing to know.
12 But they are not manually removing the spinal column?

13 DR. SCHRIEBER: No, there is no -- What
14 you have heard as well this morning, and that's the
15 standard procedure in whole central Europe, the
16 carcass is sought, and then the bones, the pieces of
17 the bones -- they are showing up somewhere, and for us
18 there is no chance.

19 If this should take place, it has to take
20 place straight away in the slaughter house. That's
21 the only place where this could be done.

22 DR. HUESTON: The last question. Do you
23 have any idea of the number of cattle exported from
24 the United Kingdom to the continent of Europe that are
25 still alive that potentially might --

1 DR. SCHRIEBER: Okay. There are some --
2 as you know, some slaughtering or killing -- better
3 said, killing programs going on. For example, in the
4 moment we are just killing in Germany all 3,000-some
5 cattle which have been exported and still there. They
6 are under control. They have a slaughtering ban put
7 on all this cattle, but now they are starting to kill
8 them to incinerate them to get rid of all this type of
9 animals.

10 I think some two years ago the Netherlands
11 has killed more than 6,000 calves which have come from
12 the U.K.

13 DR. HUESTON: Veal calves?

14 DR. SCHRIEBER: Yes. So this -- they got
15 rid of this. How many are still alive somewhere, but
16 I'm sure that in all Europe those animals, if it's
17 known that they are of British origin, are heavily
18 under control, because no country likes to risk to
19 become tomorrow a BSE country just because they have
20 not really had these cases under control.

21 DR. HUESTON: I agree wholeheartedly. Of
22 course, if you don't look, you don't find. If you
23 don't find, you don't have. Are you aware of any
24 documentation by any European country as to the number
25 of imported British cattle for breeding purposes and

1 the current whereabouts of those animals?

2 DR. SCHRIEBER: I think some three years
3 ago when the thing really boiled up, there had been
4 made an investigation. I don't know whether the
5 numbers have been really published, but even at this
6 time I became aware about the Germany numbers.

7 I'm sure that in the other countries the
8 numbers are somewhere, but, okay, they have never been
9 published. I only know the German numbers, because I
10 am in close contact with the German authorities, with
11 the Ministry of Agriculture and Ministry of Health.
12 That's normally the place you can get this information
13 from. It's not normally for public knowledge.

14 DR. HUESTON: Good. Thank you very much.

15 DR. SCHRIEBER: Thank you.

16 CHAIRMAN BROWN: I have this other image.
17 I keep getting these images. I hope you're paying
18 your sorters well. I mean, the idea of picking out
19 the occasional potato chip bag, Coke can and head --

20 Karen Hsiao.

21 DR. HSIAO: Since our charge is to ask
22 whether we're still justified to continue the
23 exemption of gelatin from the restrictions, my
24 question has to do with gelatin manufactured in the
25 U.K., because we haven't heard anything about that

1 today.

2 Is it still being manufactured? If so, is
3 it the Type A or Type B method using acid or alkaline,
4 and is it bovine or porcine derived, and is any of it
5 being imported to the United States? Are there any
6 controls on that? Does anybody know the answer?

7 CHAIRMAN BROWN: Okay, Dr. Schrieber.

8 DR. SCHRIEBER: I'm sorry. I have not
9 planned to have a one-man show today.

10 No, I have the answer. There are three
11 gelatin plants operating in the United Kingdom. One
12 is our own affiliated company. We are running only on
13 hide splits. All these hide splits are imported,
14 either from the continental Europe or from South
15 America. We are importing dried hide splits, because
16 that's the only raw material we can use.

17 The other operation working in the U.K. is
18 a bone gelatin manufacturing place, but this is only,
19 let's say, a part of the total manufacturing process.
20 So it starts in the U.K. with liming. So everything
21 is done either in France or in Belgium, because it's
22 a daughter company of a Belgium company.

23 So they are shipping over the ossein, the
24 wet ossein, which has been degreased, acidulated,
25 normally in Belgium or in France, and then they are

1 shipping over the semi-product, make the gelatins
2 there, and then they are re-exporting. So all this is
3 not U.K. origin material.

4 The third one, they are running two
5 plants, two separate plants. In one plant they are
6 manufacturing photographic gelatin from at least
7 partly U.K. raw material, but they are under
8 surveillance as well by the British authorities, I can
9 tell you. They have the inspector every week in the
10 plant.

11 The other plant is running on imported raw
12 material as well. They are using as well degreased
13 bones coming from the United States, and they are
14 buying as well some degreased bones on the continent
15 from other gelatin manufacturers. They are importing
16 as well hide splits. So this is a plant designated
17 for food and pharmaceutical purposes on imported raw
18 material, and the other separate plant at a different
19 place is running on domestic, partly domestic, but
20 only for technical applications, not for human
21 consumption.

22 That's all. There are only three.

23 CHAIRMAN BROWN: Yes, Dr. Wolfe?

24 DR. WOLFE: I'd just like to reemphasize
25 the point made a few minutes ago on the sourcing. I

1 mean, the Taylor paper referred to by several people
2 in its abstract says bioassay in rodents showed that
3 none of the regimes produced complete inactivation.

4 So I think that, if it's there, given the
5 combination of destruction of gelatin if you use some
6 of these things and the resistance of the organism,
7 that's not very good. So I think it really is
8 preventing it from getting that far.

9 Therefore, I go back to this whole issue
10 of the source. If you don't look, you don't find; if
11 you don't find, it's not there.

12 We are talking about a disease in the so
13 called natural state in this country existing in one
14 in a million people, and yet when brains or pituitary
15 and growth hormone derived there from the brains of
16 these people or given, it caused enormous amount of
17 tragedy in this country.

18 If in cows or any other species we were
19 talking about it existing in one in a million, it
20 would not easily be detected with even excellent
21 sampling. I think the figure that was used before is
22 that we have now sampled the brains of 5,000-something
23 cows in this country. That's about it, and nothing --
24 nothing has shown up.

25 That is still consistent with some level

1 of activity in cows in this country, but I think that
2 in the other countries we are ranging from none in
3 terms of sampling to some level above that. I am very
4 uncomfortable with the notion that we're saying it's
5 not okay from the U.K., but it's okay in terms of
6 source from a number of other countries, including
7 ones where there have been BSE determinations made,
8 even though the thought and wish is that these all
9 ultimately came from the U.K.

10 So I think that the issue of much better
11 surveillance and knowing what it is and that it at
12 least reaches some adequate threshold before saying
13 it's okay to make gelatin from cows or any other
14 species, but cows in this case, from these countries
15 would be in order.

16 CHAIRMAN BROWN: Yes, Linda would also
17 want to tell you that those 5,000-odd cows were not
18 just randomly selected cows, but cows that have
19 neurologic disease. So it makes the 5,000 --

20 DR. WOLFE: Right. I agree, but I'm just
21 saying that that's more than is going on in most of
22 the countries that we are still saying are okay.

23 CHAIRMAN BROWN: Much more, yes. Other
24 questions? Anything from the right side of the table?
25 Very silent today. If there are -- Yes, Larry, go

1 ahead.

2 DR. SCHONBERGER: I was just going to
3 reiterate what Sid was saying a little bit, and
4 correct a little bit of a notion that it's one out of
5 a million people.

6 It's one out of a million people -- he's
7 talking about incidence of CJD in this country. It's
8 one out of a million people per year. Okay? So that
9 if you live 70 years, the risk in terms of the idea of
10 going a whole life and not getting CJD -- the risk
11 would be to individuals much higher. So it's probably
12 closer to one out of every 10,000 deaths or --

13 DR. WOLFE: Well, since cows don't live as
14 long as people, if it were one out of a million cows
15 per year, it would be --

16 DR. SCHONBERGER: And the other issue is
17 making the distinction -- I think it was made before,
18 and I think it's an important one -- to document where
19 BSE is. So BSE countries as opposed to the concept of
20 BSE-free countries, which implies that -- what Sid was
21 talking about, that there was some surveillance to
22 document the absence.

23 I think what we're talking about in this
24 situation is probably an introduction of the concept
25 of let's define countries by BSE-free rather than just

1 who's reporting BSE.

2 CHAIRMAN BROWN: Yes. I suppose this is
3 one of the few FDA regulatory advisory committees
4 that's going to finish an hour early, and I thank all
5 of our speakers for that luxury.

6 We shall reconvene tomorrow at 8:00 a.m.
7 in this same room.

8 DR. FREAS: Dr. Brown, I'd like to thank
9 you, but I would also like to ask all the Committee
10 members -- Some of the information in your packet was
11 confidential. I'm going to ask you tonight if you
12 would take it with you and keep it with you. Tomorrow
13 morning I'll ask you to turn it in, but anything left
14 on the table tonight will be shredded. So take it
15 with you, if you need it.

16 (Whereupon, the foregoing matter went off
17 the record at 4:01 p.m.)

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