FOOD AND DRUG ADMINISTRATION

CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

+ + + + +

TRANSMISSIBLE SPONGIFORM ENCEPHALOPATHIES

ADVISORY COMMITTEE

+ + + + +

NINTH MEETING

+ + + + +

FRIDAY,

JUNE 29TH, 2001

+ + + + +

The Advisory Committee met in the Versailles Ballrooms I and II, Holiday Inn-Bethesda, 8120 Wisconsin Avenue, Bethesda, Maryland, at 8:00 a.m., Dr. David C. Bolton, Chairman, presiding.

PRESENT:

DAVID C. BOLTON, Ph.D., Chairman

JOHN C. BAILAR, III, M.D., Ph.D., Member

ERMIAS D. BELAY, M.D., Member

DONALD S. BURKE, M.D., Member

DEAN O. CLIVER, Ph.D., Member

LESTER M. CRAWFORD, JR., D.V.M., Ph.D., Consultant

STEPHEN J. DeARMOND, M.D., Ph.D., Member

BRUCE M. EWENSTEIN, M.D., Ph.D., Member

PRESENT (Continued):

LISA A. FERGUSON, D.V.M., Member

PETER G. LURIE, M.D., Member

J. JEFFREY McCULLOUGH, M.D., Member

PAUL R. McCURDY, M.D., Consultant

STEPHEN PETTEWAY, JR., Ph.D., Invited Guest

PEDRO PICCARDO, M.D., Member

SUZETTE PRIOLA, M.D., Member

STANLEY B. PRUSINER, M.D., Consultant

SHIRLEY JEAN WALKER, Member

ELIZABETH S. WILLIAMS, D.V.M., Ph.D., Member

WILLIAM FREAS, Ph.D., Executive Secretary

C-O-N-T-E-N-T-S

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

(8:00 a.m.)

DR. FREAS: I would like to ask our committee members to please take their seats and we'll get started.

Good morning. I would like to welcome everybody to the second day of the ninth meeting of the TSE Advisory Committee.

I am Bill Freas. I'm the Executive Secretary for this committee, and today's entire meeting will be open to the public.

At this time I would like to go around and introduce to you the survivors from yesterday's marathon session.

(Laughter.)

DR. FREAS: They are, starting on the audience's right-hand side of the table, Dr. Donald Burke, Director of the Center for Immunization Research at Johns Hopkins University.

Now at the right-hand side of the table is Dr. Elizabeth Williams, professor, Department of Veterinary Service, University of Wyoming.

Next is Dr. Jeffrey McCullough, professor, Department of Laboratory Medicine and Pathology, University of Minnesota.

In the empty chair which will soon be filled will be a temporary voting member for today, Dr. Stan Prusiner, Professor of Neurology, University of California, Institute of Neurodegenerative Diseases.

Next is a standing committee member, Dr. Peter Lurie, medical researcher for the Public Citizens Health Resource Group, Washington, D.C.

Next is our consumer representative, Shirley Walker, Vice President of the Health and Human Services Dallas Urban League.

Next is a standing committee member, Dr. Dean Cliver, professor, School of Veterinary Medicine, University of California-Davis.

Next, Dr. Steven DeArmond, professor, Department of Pathology, University of California-San Francisco.

Next, Dr. Suzette Priola, investigator, Laboratory of Persistent and Viral Diseases, Rocky Mountain Laboratories.

Next is a temporary voting member for today, Dr. Lester Crawford, Director, Center for Food and Nutrition Policy, Georgetown University.

Next is the Chairman for today, Dr. -- Chairman of the committee. Excuse me -- Dr. David

Bolton, head of the Laboratory of Molecular Structure and Function, New York State Institute of Basic Research.

(Laughter.)

DR. FREAS: Next is Dr. John Bailar, Professor Emeritus, Department of Health Studies, University of Chicago.

Next is Dr. Ermias Belay, medical epidemiologist, Center for Disease Control and Prevention.

Next is Dr. Lisa Ferguson, Senior Staff Veterinarian, U.S. Department of Agriculture.

Next is Dr. Peter Piccardo, Associate Professor, Indiana University Hospital.

Next is Dr. Paul McCurdy, consultant to the National Heart, Lung, and Blood Institute, Bethesda.

Next is Dr. Bruce Ewenstein, Clinical Director, Hematology Division, Brigham and Women's Hospital.

Next is Dr. Stephen Petteway, who is a guest from industry. He is Director of Pathogen Safety and Research, Bayer Corporation.

I'd like to welcome all of you this morning.

I read the entire conflict of interest statement into the public record yesterday. Today I am going to read a few excerpts that do pertain to today's topic.

Pursuant to the authority granted under the committee charter, the Director, Center for Biologics Evaluation and Research, has appointed Drs. Paul McCurdy, Stan Prusiner, and Lester Crawford as temporary voting members for today's session.

Based on the agenda made available, it has been determined that the agenda addresses general matters only. General matters waivers have been approved by the agency for all members of the TSE Advisory Committee, as well as consultants to this meeting. The general nature of the matters to be discussed by the committee will not have a unique and distinct effect on any of the member's personal or imputed financial interests.

In regards to FDA's invited guests, the agency has determined that the service of these guests are essential. The following reported interests are being made in regards to today's guest to allow meeting participants to objectively evaluate any presentation or comments made by the participants.

Dr. Robert Rohwer consults widely on TSE

issues with both the blood industry and the gelatin industry for which he receives compensation. His laboratory and research program receive support from the Gelatin Manufacturers of Europe.

Dr. Michel Schoentjes is employed by SKW Gelatin and Specialties in France. He's also Vice President of the Gelatin Manufacturers of Europe.

In the event the discussions involve specific products or firms for which FDA's participants have a financial interest, the participants are aware of the need to exclude themselves from such involvement, and their exclusion will be noted in the public record.

A copy of the waivers are available by ordinary request under the Freedom of Information Act.

Dr. Bolton, I turn the meeting over to you.

CHAIRMAN BOLTON: Thank you, Dr. Freas.

This morning's topic is an update. It is presentation by industry of interim results of a new study on the inactivation of TSE agents by the manufacturing process of gelatin and -- I've just been reminded that we actually missed a presentation in yesterday's marathon. Let's see. Where was it inserted?

Do you have the modified agenda from yesterday? I think we're going to try to squeeze that in this morning before we start. There we go. Excuse me.

And that was a committee update on a summary of DHHS action plan on BSE and TSE by Dr. Stephen Nightingale, and we will have that now before we begin Topic 3.

Dr. Nightingale.

DR. NIGHTINGALE: I almost got away without giving this, but not quite, and I'll go as quickly as I can.

Good morning. Thank you for the opportunity to present the Department of Health and Human Services bovine spongi -- BSE/TSE -- I think we all know the words -- action plan.

May I have the next slide, please?

This was approved by the Secretary on June the 18th. It was developed under the direction of Dr. Lawrence who's the Acting Principal Deputy; Assistant Secretary for Health, seven words and a title that's quite a title. Those who contributed to the formation of this report are included on the slide, but like the notes, the margin is not wide enough to contain all of the people, and I apologize for those who are not on

the list.

The basics of the plan can be put in a very straightforward fashion. The task of surveillance is primarily that of the CDC. The task for protection is primarily that of Food and Drug. The task of research is that of NIH. And the task of oversight is the Office of the Secretary. That is, of course, the paradigm that could apply to many, but it applies to this one in particular.

May I have the next slide, please?

A very, very brief review of the surveillance activities, and Dr. Belay, one of the participants, is in the audience who could expand on this, is the basic component, the basic CDC's activities are based on ongoing relationships, and I'm quoting from the plan itself. The committees have copies of it, and the public can obtain copies of it out at the front desk.

Ongoing relationships with state and local health departments and with institutional individual providers and institutions. Dr. Belay could explain this better than I, but this is truly the backbone of what the CDC does, and I wish more people understood it because there is more than Dr. Schoenburger and Dr. Belay who are involved in this activity, and those

thousands of people are included among those who would not fit on the acknowledgements of this report or plan.

The CDC surveillance activities are supported by the National Prion Disease Pathology Surveillance Center, Case Western University; began in 1996's investigations of CJD deaths at age less than 55.

Next slide.

The plan for expanded surveillance is cooperative agreements with state and local health departments to increase pre-mortem surveillance in order to increase post mortem examination of those at increased risk of variant CJD, for example, ataxia, dementia, foreign residence, or food exposure.

What I've tried to do was get the key phrase that Dr. Belay and Dr. Schoenburger has contributed to it. This is not the entire plan, but as best I can in ten minutes, this is the core, is get at the cases before they die so that adequate data collection can be obtained at the moment when it becomes available.

I hope I've done justice to the very substantial efforts that you guys do, and at the same time to increase laboratory support both at Case

Western Reserve University and on the main campus in Atlanta in anticipation of increased demand for back-up pathology services.

And finally, to review and update current infection control guidelines for patients and health care workers.

That is the last of two slides. I realize there is more, but this has been a long meeting. May I have the next slide, please?

Protection is primarily assigned to Food and Drug, but as Food and Drug pointed out repeatedly throughout the preparation of the plan, they do surveillance as well. The lines are not as neat as we would like, but they are as neat as we need them to be.

The core that I extracted from the FDA section is to continue and is necessary to expand import and animal feed surveillance, inspection, and enforcement actions -- I'm sorry -- import and the feed surveillance, inspection and enforcement actions to control the use of mammalian protein in ruminant feed, keep potential infectious products out of the United States, and address the issue of chronic wasting disease in domestic and elk.

If I could have the second slide.

That sentence can be applied to a lot of activities, and Dr. Asher, who was a major contributor, I hope will understand that I have tried to summarize rather than to recite the plan.

The areas where FDA has protection include -- and I think maybe I've got them all here -- blood products, plasma derivative, transplanted tissues, vaccines, other biological drugs, devices, cosmetics, human food, human food additives, dietary supplements, and the one that I extracted on the previous slide, animal food. This is not a trivial undertaking. If I've summarized the activity by continue and, as necessary, expand, I hope I've got the essence of what we're trying to do here.

If I may have the next slide.

And in addition, a very important component of what FDA wishes to continue and, as necessary, expand is consumer communication and education, and maintain as necessary or possible, I suppose you would say, expand the regulatory research agenda, which includes tests for the infectious transmissible particle -- I guess that's the right word -- and inactivation of that agent.

If I may have the next slide, please.

In research at the NIH, to summarize the

portfolio very briefly, the pathophysiology of human and animal prion associated diseases, methods of transmission within groups and across species, diagnostic test development, and preliminary work on therapeutic strategies. I suppose that would be everybody's general agenda for this.

But specific actions by the NIH, establishing a repository for research reagents in the next fiscal year; to double laboratory facilities available over the next two years; to triple the number of investigators in TSE research over the next five years; and double or, if possible, triple current spending for TSE research over the next two years.

One of the questions that came up in the preparation of the report was where are your deliverables. You are looking at them.

Next slide, please.

And in addition, for the component of the research agenda at the NIH, the Acting Director, Dr. Kirshstein, plans to convene special meetings -- well, we plan to convene special meetings to identify the major needs and opportunities for research in BSE and TSE both in academia and in industry, a point to which I will return in a minute, and the scientific quality of the applications will determine the total funding

for this initiative, and there is in the report the consideration of establishment of prizes for achievement of major milestones.

One always hopes that that will not be necessary, however, not just for budgetary reasons.

The oversight by the Office of the Secretary. There has been established under the leadership of the Commissioner of Food and Drug an interdepartmental steering committee for BSE/TSE affairs. It's chaired by Dr. Schwetz (phonetic), and has representatives -- this is a test for those of you who don't live in Washington, and I've made the test easier for you because I did not give you the acronyms -- for the State Association of Feed Control Officials and National Association of State Departments of Agriculture, nor for that matter for Customs or State. The rest of the acronyms hopefully will be known not only to the Beltway insiders.

The point here is that on a regular basis, roughly monthly right now, all of these agencies, Commerce, State, Defense -- yeah, Defense is on there -- as well as Health and Human Services and government consumer representatives do meet on a regular basis to maintain oversight of this issue.

May I have the next slide, please?

And the goals of the oversight or coordination of policies and activities among agencies, including risk communication -- if I knew how to do bold on Power Point, I would have made a bold issue there. I would have "bolded" it because that is now an ongoing concern of the department, to make sure that the public is aware on terms that it can not only understand but deal effectively with what the government is trying to do and to integrate our contingency planning.

You've heard at this podium before I came to it thoughts about what would we do if there is a case of BSE or a case of variant CJD in the United States. That's up there. It is a responsibility that we are aware of and are responsible for.

And identification of potential vulnerabilities of the United States to prion pathogens and development of responses to such situations. That is obviously an ongoing task.

May I have the next slide, please?

There has been another proposal submitted to the Secretary. Dr. Prusiner was an author of it, and this is up here to acknowledge and to thank Dr. Prusiner and his colleagues because it was, quite bluntly, a stimulus to us, and it was appreciated on

that basis, and Dr. Prusiner will have the opportunity to comment. I hope his comments will be supportive, but part of my job is to receive them.

May I have the next slide.

To summarize our take on the proposals, we believe that both proposals share a common vision and enunciate common goals. If there's a major difference, it is that Health and Human Services basically proposes doubling of NIH research funding by 2003 and the Red Cross proposal is for about ten times that amount, 250 to 350 million.

Now, Health and Human Services seeks input from both academia and industry to identify additional research projects and additional resources, both human and physical, that could be recruited to this effort.

When the Secretary signed this proposal on the 18th of June, he signed -- when he signed the action memo endorsing the plan, which is how these things are done in our circuitous way -- he also signed an endorsement to convene a meeting of industry representatives in his office. I mean, it's a term we're going use loosely. It's an office. It's a nice office, but it's not that big -- to seek input from industry on two things.

The first is what research is there that

we're not doing, either that we're not doing or you're not doing, you, industry, and ought to be done, which is probably the easier of the two questions.

The second one is where are the additional human and physical resources that are necessary to do it. You saw part of the plan would, I think, double the investigators in five years. I only know it takes four years to go through medical school. Dr. Rohwer has told me repeatedly how long it takes to get to where you need to be in this field, and there is an appreciation that it takes longer to get to where you need to be in this field than in other fields because the mice only get sick so fast.

And at the same time, it's hard to get where you want to go in this field because you cannot do this on the corner of a lab bench. We recognize the unique, well, the specific, I guess I would say, barriers to making progress in this field and will seek input.

I would have liked to have had this meeting before the first of September. Realities are people take a break. People need to take a break, and I just don't see it happening before the first of September, and that's not just because the Secretary's schedule is crowded before then, but there will be

telephone calls, and part of the telephone calls will be to the list.

I think Dr. Freas, as part of his responsibilities, does identify individuals and industries who may be potentially conflicting for this meeting. That's a quick and dirty source of contacts, and I'll do secondary contacts, and the reason I'm up here at eight o'clock and taking a little more than my allotted time is to try to communicate to the community through this audience that we really do want to hear from you.

We anticipate that probably the big companies would much rather pay for their own research than go through the hassle of writing an RO-1, but we don't know, and we'd like to find that one out.

Finally, if I could move on, very quickly I'd like to in the last 30 seconds allotted to me here expand slightly, if I could, on the subject of the monitoring of the blood supply because that was a substantial component of your discussions yesterday.

What are we going to do? And, very quickly, where did we come from on this? In December '97, we became aware of acute shortages of plasma derivatives. In April of 1998, we had an Advisory Committee on Blood Safety and Availability. That's

what that acronym stands for. This meeting made a number of recommendations and received the support of the plasma industry for regular monthly monitoring of the supply, which began full time about October of '98.

They started out in August '98, but we have had and the public has had, a very important point, monthly records of the inventory and distribution. Inventory and distribution is a point you're going to hear over again, of plasma derivatives for albumin, intravenous immunoglobulin preparations, in aggregate the various plasma Factor 8s and recombinant Factor 8.

In February of 1999, the National Blood Data Resource Center published a report that estimated that in the year 2000 demand would exceed supply for blood. That occasioned a second Advisory Committee meeting, which in turn occasioned the Surgeon General's Task Force, which led to an amendment to the FDA's -- next slide -- blood action plan, which in turn led to a contract to NBDRC for monthly monitoring of the supply of blood in the United States. That is a contract -- I'm going to jump over here for a minute -- that for a variety of reasons has been transferred to the Office of the Secretary, and that is for the

time being where responsibility for these monitoring activities resides.

We do not know whether that will be permanent. That's not in Transportation, and it's probably a good thing that it's not.

Finally, the news of the BSE spread throughout Europe, occasioned yet another meeting to determine whether or not our monitoring of the blood supply was going to be adequate for policy and public information purposes.

Basically we determined that it was not. Supply is half of the equation. Demand is the other half of the equation, and that is assuming that there is not a third or a fourth or a fifth half to the equation. So we're moving to the second with the next slide, please.

What we are initiating with a combination of money left over and an agency tap is a pilot project that will go from July 1 through September 31st basically to measure supply. The idea is that there will be sentinel sites, a total of 29 of them, in the Northeast, South, the Midwest, and the West, in the four regions.

We have sent out 17 contracts. Dr. Ewenstein and I had a conversation, so I can identify

that Brigham and Women's is willing to sign their half of the contract, trying to draw a find line between information and review and making eye contact with some other people.

Dr. McCullough will be another contractor, just to move on. I think the sites Boston, Pittsburgh, Washington, and obviously New York. We're going to double sample New York, two hospitals in each community. We're going to put aggregate data out on the Web for regions rather than individual hospitals, and we do have a Web site that is secure from the moment your finger hits the keyboard, to which we will put it.

We're going to ask the sites to put this up as a standard operating procedure. I mean, we love each other and we trust each other, but if the reporting is a standard operating procedure, then you've got validation of your data, and you have public confidence in the data, which to me is an extremely important point.

We are going to ask on a daily basis -- it doesn't matter if it's 12:01 a.m. or 10:00 a.m. -- but how many units of A, B, AB, and O positive and negative and platelets, apheresis, and random are in the frig. This is total inventory, including

consigned inventory because consignments fluctuate back and forth.

We'll get daily inventory, plus the next is how many units were transfused, how many went out the door, how many were exported to another site, say, in your region, and how many were outdated. So we'll have inventory and out-flow from which we could calculate days of supply for each.

But there are some complications to that days of supply. Monday is different from day of supply on Friday. So that is why this is a private -- there will be very active collaboration not only by the investigators, the participants, but we hope by the public at large, but the key is going to be a daily event log.

What we are asking for every day is the answer to a simple question. Describe any actions taken in the previous 24 hours in response to discovering that supply of blood or platelets was insufficient to meet demand.

If that field is blank, we're okay. If that field isn't blank, we've got a problem, and the idea is to identify where those problems are. This is the initial data set we'll try to use to answer it. Compare the data set, and we will go from there.

May I have the next slide, please?

Product development. I would emphasize ongoing consultation with industry professionals. My boards are in nephrology. I do AIDS work, and I'm a bureaucrat. My job is to coordinate the needs both of the government and the expert opinion of the public.

We will have an Advisory Committee meeting, Blood Safety, on August 24th in which I will get up and solicit criticism. I hope I can take it. I've seen some of you take criticism yesterday. I hope I'm as tough as you are, but we need public scrutiny of this enterprise both to make it valid and to make it useful.

I'll also be at the AABB. There will be another chance for public comment at that time and hopefully that process will continue. We may take a six month extension until we get it right, but the idea is to get it right and get it out for public long-term contract under full Federal Acquisition Regulations.

And finally, extend this to plasma derivatives as quickly as we can. I think that's the last slide.

But parallel activities, we will continue the PPTA and NBDRC blood supply monitoring, consider

improvements based on experience, evaluate the use of publicly available databases to monitor and project demand.

I do have a full-time detailer, Dr. Barbara Silverman from HCFA. Briefly, she is very good. This is tougher than it seems.

The April paper by Paul Ness (phonetic) and colleagues in Transfusion talks about some of the limitations of the databases, and we're going to do a validation study to try to replicate some of Paul's work.

But the answer is that's not as simple as it seems.

Ongoing consultation with stakeholders.

And the last slide, please.

To what end? The Red Cross has asked me that repeatedly and bluntly. That answer is a simple one. We need to communicate to you all what the real supply of it is. We need to use communication to achieve consensus (a) that there is a problem and (b) on what to do, and the third one is action.

And I'm out of here.

CHAIRMAN BOLTON: Thank you, Dr. Nightingale.

Any questions? No? Don.

DR. BURKE: The 29 sites that are going to be studied, are any of those Red Cross sites or are they --

DR. NIGHTINGALE: I'm sorry. These are all hospital transfusion services. We already studied 26 supply sites. NBDRC's contract is for a representative sample of producers, and that's how we measure supply. This is for 29 sites how we measure demand.

DR. BURKE: Okay. Thank you.

CHAIRMAN BOLTON: Dr. Crawford and then Dr. McCullough.

DR. CRAWFORD: Yes. This is obviously a national program for Department of Health and Human Services. Two points. One, will there be an initiative to unify all the departments of government in this program, such as USDA and defense?

And secondly, what individual will coordinate this overall effort?

DR. NIGHTINGALE: The coordination right now is through the Interagency BSE. FDA put that together some time ago, and we feel that that coordination is adequate right now. All the agencies meet on a regular basis, and people do schedule their meetings around it.

Do you have meetings, say, between the Secretary of Health and Human Services and the Secretary of Agriculture?

I mean, in February when there wasn't much going on in the first days of the new administration, that seemed like a really good idea, but in March when we got back to the previous levels and the calendars filled up, that seemed like a less good idea. So probably that's why we haven't done it.

CHAIRMAN BOLTON: Dr. McCullough.

DR. McCULLOUGH: Steve, I actually thought of making a motion, and I'm told that procedurally this is not the time to do it, but I think the action that we took yesterday may very well this time create a substantial supply problem, and so you mentioned the proposal for expenditures through the Secretary's office, and I would just urge that the Secretary consider making a series of one time grants available for innovative proposals in blood donor recruitment.

And I can follow this up with a letter to you because I think over the next 18 months continuing to send letters and call donors we've been doing for 40 years, and I think we're going to need very innovative thinking in order to deal with the situation over the next 18 months.

DR. NIGHTINGALE: I have to walk a fairly narrow line here because I am not supposed to solicit such proposals.

DR. McCULLOUGH: No, I just brought it up. You didn't solicit.

DR. NIGHTINGALE: I didn't plant the question.

DR. McCULLOUGH: No.

DR. NIGHTINGALE: But the Secretary -- America's blood centers and others have proposed to the Secretary a plan in roughly the amount of $10 million in the coming fiscal year for innovative grants, and one of the suggestions has been made that this operated roughly at least for the first year in parallel to HRSA's organ donor recruitment efforts, which procedurally have been quite successful.

There is support within the Office of the Secretary for that proposal.

CHAIRMAN BOLTON: Dr. Lurie and then Dr., Prusiner.

DR. LURIE: As I took the action time, what I mostly heard that was new was more about the surveillance system, more about research at NIH, some new meetings, which are all important to do, but I guess what I'd like to hear from you is what you're

doing about some of the more concrete issues in BSE and VCJD prevention in this country, and in particular two of them.

One is progress on the policing of the feed ban, where a significant fraction of the renderers and manufacturers and so forth have not been adequately or even at all inspected.

I guess related to that, whether there's any discussion as has sometimes been intimated by FDA officials of extending the feed ban in particular ways or removing particular exemptions, and then the second area would be about dietary supplements, what concrete action, you know, the Agency, I guess, defined in HHS is planning on doing on those things.

DR. NIGHTINGALE: I'm certainly going to have to apologize that I am not prepared to give you a detailed response to that. If we could at the break discuss who the most appropriate federal official would be for it, but those are not my areas of immediate expertise, and I do make a commitment to let's talk, and we'll find the people who can give you the answer to the question. I'm just not that person.

DR. PRUSINER: Excuse me. I'm delighted to learn about the NIH's plan to double laboratories, triple funding. It fits with the document that you've

passed out that's prepared with my colleagues for Secretary Thompson.

What I'd just like to add is that the reason that we saw a much bigger need than the NIH is willing to fill at this moment is that I think -- and it really, I think, reflects on the conversations yesterday in this committee. We constantly didn't have enough data to make informed decisions. It's because we don't have good enough tests. It's because we don't understand the details of these diseases sufficiently.

And my hope -- it's not a dream; it's a hope -- is that we will do much more at the scale that we have proposed than the current plan calls for so that we can get this information. We can not only train young people, as you were alluding to, which is extremely important, but we can entice people who are extremely good scientists and well established to move into this field.

And I would like to stress that I think it is the long-term funding, the long-term program which is the only way to entice young people to get into this field and to ask some people -- to entice some people, I should say, not to ask them, but to entice them to make career changes because there is no

question about the interest in the area. It is a matter of funding.

DR. NIGHTINGALE: That suggestion has been received with respect, and I hope that my presentation reflected that respect.

DR. PRUSINER: It did.

CHAIRMAN BOLTON: Dr. Nightingale, I can see that this is a broad, interdepartmental plan. Where does the responsibility for implementing this plan lie? Does it lie within DHHS?

Who's going to make sure that things happen? Certainly not the committee that oversee it.

DR. NIGHTINGALE: I think that's a fair statement, and, by the way, the Secretary of Health and Human Services, what you see there, number four, oversight, I may have slung that past a little bit too fast and said a little bit more about the coordinating committee because on a day-to-day basis, this is not something that's going to go into the Secretary of Health and Human Services' Office. If you try to manage this from the Secretary's office, it will fail.

I'm watching several such attempts right now, and this is not Republican or Democrat. Everybody wants their plan to be at the Secretary's office. Hopefully what will happen is that this will

come up to the Secretary's office for regular review, and I am the conduit. I am the Office of the Secretary representative to that steering committee.

When something goes wrong, it goes to the Secretary. As long as things are going right, it's the Steering Committee.

CHAIRMAN BOLTON: thank you.

Any other questions?

(No response.)

CHAIRMAN BOLTON: Thank you, Dr. Nightingale.

Okay. Now we will move on to topic number three, which is the update of the interim results on a new study on the activation of TSE agent by the manufacturing process of gelatin, and I just want to tell the committee that it's our pleasure this morning to be talking about science and not about policy. So we don't have to be sitting here thinking about what decisions we have to make or how this is going to influence a vote on some question.

But what I would like you to consider is as the representatives present the data, to consider the study design and prepare in your mind any questions you have about the way the study was designed, and to also consider what information, in

addition to what's presented or within what's presented you would need to make policy decisions once these studies are completed and the information is presented in whole to us to begin our policy recommendations.

So with that, we'll begin with Dr. Yuan-yuan Chiu, who's from the FDA, and she will introduce the topic.

Dr. Chiu.

DR. CHIU: Good morning. Can you hear me?

Good morning, Dr. Bolton and members of the committee.

Dr. Bolton said we're not going to discuss policy this morning. However, in order to help you to understand how we get to here, so I'm going to give you a brief summary on the evolution of gelatin policy.

Next slide.

All right. We have the BSE academic, the United Kingdom, early '90s. The agency has issued a series of letters to industry in the period of 1992 and 1993. In the letters the agency has request the industry not to use bovine derived materials derived from cattle which have resided in or originated from BSE countries.

The letters were later published in the Federal Register notice in August of 1994. The letters to the food and cosmetic industry stated the milk, the dairy derivatives, and the gelatin are exempt from this policy.

However, in a letter to the pharmaceutical industry, we did not state that gelatin was exempt. So, therefore, it raised the question from the pharmaceutical grade gelatin manufacturers about their status. So at that time, the agency reviewed the information available and then made a decision and issued a letter on July 1st, 1994, to the gelatin industries, stating the agency does not object to the use of bovine derived material from BSE countries in the manufacture of pharmaceutical grade gelatin.

At that time, the Gelatin Manufacturers of Europe also started to come back with a validation study to determine the inactivation capability of the manufacturing process.

Next.

Early in 1996, the British government announced the discovery of the ten new variant CJD cases which might be associated with BSE. With that information, the agency then in May of 1996 issued another series of industry letters to alert the

industry of the new VCJD information from U.K. and to reiterate the earlier recommendations.

So at that time then the gelatin was still exempt from the requirement.

During the same time, around the same time, then the agency received the validation study without from the GME. After reviewing the data, the agency decided those data should be shared with our Advisory Committee.

At that time we only had a CJD Advisory Committee. So the agency decided to convert the committee to a TSE committee. So that would cover all of the TSE diseases, not limited to CJD.

So on April 23rd and 24th of 1997, we had the first Advisory Committee meeting. The topic brought up to the committee was on gelatins. The manufacturing process, the inactivation studies were thoroughly reviewed, and with the deliberation of the committee, the agency then went back to evaluate the safety of the gelatin, and at the same time, the GME committed to conduct a second study.

This is the second study we're going to talk about today.

Next slide.

So after the internal review and

evaluation, the agency decided we should really approach the gelatin safety based on its route of administration to humans. So in October 1997, the agency published the gelatin guidance and made the modification to our policy.

The modification includes the remove of exemption of bovine bone and hide gelatin derives from BSE country; the manufacturing of injectables, ophthalmics, and the implanted products.

With regard to oral and topical use of gelatin, the agency recommended several safeguards. One of them is to use BSE-free herds, and they also recommended the removal of spinal vertebrae and spinal cords from the bonds of the bovine material sourced from countries with reported BSE cases or at high risk of BSE.

So this is the current policy implemented since 1997.

In April 15th and 16th of 1998, the TSE Advisory Committee met again, and we introduced the gelatin guidance, and the agency described the changes regarding to the injectables, ophthalmics, and implanted products, and also introduced the safeguards recommended for oral and topical use of gelatins, and the recommendation in the gelatin guidance was

accepted by the committee.

Next slide.

So recently the agency has received two reports which describe the interim results of the second gelatin study. Last week the agency also received a third report, which is also in your package, and so therefore, here we're today to discuss the interim results because they are preliminary data and, therefore, the agency felt it's too early to make a decision just based on interim data. Therefore, we would like to share the information with you, but we felt to ask you to make a recommendation would be premature.

That's why we have not formulated the questions specifically for you to answer, and we will be looking forward to listening to your discussion.

Thank you.

CHAIRMAN BOLTON: Thank you, Dr. Chiu.

Are there any questions for Dr. Chiu?

Peter.

DR. LURIE: Can you just clarify to what extent the existing guidelines make a distinction between gelatin derived from bone and gelatin derived from hide?

DR. CHIU: With regard to bovine gelatins,

we do not distinguish bone from hide. If you looked at prohibition for injectables, implanted products, and ophthalmics, it was stated bone and hide gelatin from bovine source. So we do not distinguish that.

With respect to topical and oral use, we do not distinguish bovine bone and hide, but we do distinguish porcine gelatin from bovine gelatin.

CHAIRMAN BOLTON: At one time wasn't there a differentiation between bone and hide?

DR. CHIU: Because we believe during the slaughtering of the cattle the hide could be contaminated with neural tissues.

CHAIRMAN BOLTON: Maybe I'm misremembering. I thought at one time that there was.

Any other questions?

(No response.)

CHAIRMAN BOLTON: Okay. Thank you very much, Dr. Chiu.

Our next presentation will be by Dr. Michel Schoentjes, and he will present the European view of the European Gelatin Manufacturers.

Dr. Schoentjes.

DR. SCHOENTJES: Mr. Chairman, ladies and gentlemen, good morning. First of all, I wish to thank you to give GME the opportunity to make

presentation, through thanks to Dr. Rowher about the latest results of the global study still going on and of which we have early details.

Before we get the scientific results, I will give you a brief summary of the situation in terms of safety of gelatin vis-a-vis BSE because this has obviously evolved since '97 when we had this more outstanding discussion.

Next, please.

First of all, a small reminder. Who are GME? GME, Gelatin Manufacturers of Europe is an association representing 11 members, companies operating 27 gelatin plants around the world, including three in the U.S. and three elsewhere outside Europe or U.S.

In Europe themselves, they produce about 45 percent of the world production of gelatin,a nd this gelatin is of all current available types. The main ones are from bovine bone or hides, as was just said; also from porcine bone and hide; and then a few other less important in volume from other raw materials, like fish skin, for instance, and there are a few further being developed because of all of this context.

Next, please.

What are we talking about when we're talking about gelatin vis-a-vis a concern with BSE? In this table, you can see I have put on left-hand side two main processes, on the right-hand side the four main sources of raw materials, what tissues are being used from what animals.

And in the box you find is there a concern, yes/no, about the possible risk which you see, and also in what kind of application are these types of gelatin being used.

Clearly, in here you will see that the concern is only with bones from bovine or ruminants in general. All the other we will not be talking about, considering that our concern today is especially vis-a-vis the TSE.

Now, what is one of the concerns that we discussed with FDA? That is that in the United States there is a good deal of importation of bovine bone -- that's the right-hand side column -- bovine bone gelatin that is used for the pharmaceutical industry and in the paramount for the capsule industry, and as you know, capsules are very popular both for actual pharmaceuticals and for dietary supplements.

In this the concern was do we really need in the United States to import this gelatin. Well,

when we looked at this table, the need for the capsule industry in the States is about 10,000 metric ton of gelatin. There is a variable produced in the States from U.S. source bones, about 5,000 tons of this gelatin. So they are missing another 5,000 tons. This has to be imported because the production capacity of the American gelatin industry for the time being is limited to this.

It was much higher in '97-'98 when we reviewed this. This is half and half. It used to be 80 percent/20 percent.

Traditionally this gelatin are coming from European plants, and it's still going on this way, and it's imported with special permit from USDA since the '93 restricted rules from the FDA, and also with some formal certification from the manufacturers and so on with all this, et cetera, for the compliance with the October '97 guidance that Dr. Chiu just talked about.

Now, if we have to import, at least can we do it from U.S. sourced bones? So going back, and that's a little bit more of an industrial calculation, there is a need for this 10,000 metric ton of gelatin for the capsule industry in the States. The domestic production of degreased bones in the States is about 130, a little more, 130,000 metric tons.

But from these bones -- and we are dealing with bones here -- from these bones used for photography worldwide, broadly in the States, but also in other places like Europe and Japan, there are already 90,000 tons being used, used for capsule and pharmaceutical manufacture outside the U.S., and that is, again, Europe, Japan, et cetera. There are about 15,000.

So left available for making capsules, for gelatin for capsules inside the U.S., about 28,000 tons. So there is a lack of a good 30,000 tons of American bones for making gelatin whether in the States or outside for the capsule industry.

So we have to source bones elsewhere, and there we're looking for non-U.S. bones in Asia, Africa, Europe, and that's the question today. The availability are limited. As you can see here, I put selectively compliant because in certain operations it is compliance. In others, it is not. I'm speaking on behalf of GME. So I cannot quote the one or the other, but this is available, of course.

Okay. Next.

I have in this chart, necessarily important, it can change every six months or so, but it's important because it gives you a review of the

major constraints of a different source of bones.

Here are the origin of the bones that can be used and are currently used for making gelatin. You have United States, South America, Australia, New Zealand, and a few other smaller countries. These are the countries where no BSE has been reported, and they are categorized as no risk of BSE being present by European Scientific Steering Committee.

In Europe, Asia, Africa. Asia is a traditional source, especially with Pakistan and India, of course, and today there is also People's Republic of China, but we have not included that in here because they are consuming all their bones themselves.

Okay. The quality, well, just actually the source of the bone. Typically there are some porcine in European bones. Restrictions vis-a-vis USDA '93 restrictions also mentioned. FDA -- when I say "FDA," I'm referring to the '97 guidance -- compliant, compliant, selectively compliant, some are. Compliant, 420,000, compliant for 10,000.

This is important. There is a little note there. This is what is compliant to the knowledge of GME because they actually control audit, have contract conditions with the suppliers.

In Asia, India, Pakistan, and the same applies to Africa, they are much more available, especially in India. They're a very huge industry, but they don't apply necessarily the same restrictions and the same, say, conditions that Gelatin Manufacturers of Europe apply to them.

Okay. This is for American rule. This is European rule. Category, that's geographical, BSE risk evaluation, Category 2, 1, 1. One is free, definitely free with no hesitation. Two is free, but possibly there is a risk.

You see the United States is two. Only this country is number one, and this country, number one, we talk about the limited supply because I can guess your reaction immediately.

Removal of specified risk material all the way through, that's easy. Spines which have now become specified risk material in Europe for a few months, they are not removed in this origin. They are now, and that's in progress, and they are here as well.

And here also refer to the European Pharmacopeia, and the Pharmacopeia has actually adopted the note for guidance issued by the European Medicine Evaluation Agency where they have made a

complete recommendation for the gelatin. All of this is compliant as well.

Now, when we look to the availability, keeping in mind that we need about 30,000 metric ton to complete the lack for the American capsule industry, we see, well, we have here the total that we've been working on. Number one, which looks attractive, we have only 6,000 tons available roughly, and that's stretching even.

In Europe, there is porcine bone marrow available more and more, and the bovine, there is a good deal which is now also completely compliant, not all of it, and for Asia and Africa, we have about 30,000 tons, and that's where we have to work.

I cannot say which member company of GME is sourcing this in this place. This is to be arranged with individual customers for gelatin, but that is where the gelatin is sourced from to complete the 30,000 tons missing, and that's the issue, of course, of concern to FDA.

Now, the background -- may I have the next slide, please -- the FDA guidance deals, of course, a lot with the raw material, as Dr. Chiu just said. In Europe and for all the plants operated by the European Gelatin Manufacturers Association members, we use only

raw materials from healthy animals slaughtered in slaughter houses declared -- the animals, of course, not the slaughter houses -- fit for human consumption with a post mortem inspection, certified, documented traceability from the gelatin, finished gelatin, all the way up to the slaughter house, audit by and the Gelatin Manufacturers audit by veterinary authorities, the supplies of it also by the gelatin producers.

And the sources are taken according to the classification GBR that have been showing on the previous table, summary table there.

Thank you. Next, please. Now, oh, I skipped one maybe. Yes, sorry.

Now, when we go to the regulation controlling the gelatin industry, first, a reminder. In Europe, contrary to the United States, food and feed products, on one hand, pharmaceutical, cosmetics, medical products are regulated by different authorities. That means that the idea of FDA regulated products under the responsibility of FDA is, in fact, split in a different way in Europe, and these authorities also have different behavior, just as a background.

Now, for food grade, and here I will explain how it works, there is a major decision that

is in 99/724, which gives a global rule, really good manufacturing practice specifically for gelatin. How do you do it, all the way through; I have a slide on it, and if you want to have more questions, anyway, I will show it briefly afterwards.

It requires, of course, registered premises obeying to a series of rules. It gives two typical constraints as far as TSE is concerned, but it gives all the rest, as well, and also it is influenced by this decision, which is a recent one, as you see. That's the new specified risk material rule prohibiting the use of skulls, brain and everything for whatever, human food or animal feed is concerned.

For pharmaceuticals, the situation is different. The gelatin being a ruminant product, possibly presenting a risk for BSE, in order that it can be used in pharmaceutical, they define with a marketing authorization. The gelatins, like other ruminant products, have to go through a certification by submitting a complete dossier of the manufacturing process, the source of raw materials, the plant where it's manufactured, et cetera.

Some kind of marketing authorization of itself, but it's a certification, and this certification is done by the European Directorate for

the Quality of Medicine, which depends -- it's a branch of the European Pharmacopeia.

All of the constraints there is just to demonstrate that this very product, in this case bovine gelatin, complies with all the recommendations from the EMEA, European Medical Evaluation Agency, that you comply with all of these recommendations.

And it's important. I have another slide on these recommendations, but this decision, the last one, just tells you it's a one-sentence decision that all product presented for BSE should comply with the recommendation from EMEA.

Next one.

That's for a change. To summarize this regulation, you have the food, the farmer, bovine product, porcine. Okay. This is dealing with BSE constraint. This is more of a religious constraint. So for both this type of gelatins, you have the general standards of the finished product. Okay. Here it's the Pharmacopeia, U.S., Europe, Japan, what have you. Here it's all the standards for the food products that you have around the world, including the Codex, of course, the food Codex. So that's global.

Now, for the food gelatin covering all grades of gelatin, you have to comply with this 724

giving all the rules. So that's, again, what I said.

For the food, you have also the influence of the specified risk material regulation, but that's only for BSE and only for bovine or ruminants, and on the other hand, you have symmetrically, of course, the general. You have for BSE the European Pharmacopeia with the EDQM certification of compliance, with this famous note for guidance, and that's the obligation.

And I have put here in between the situation with FDA because FDA runs on both sides here. It's only dealing with the BSE issue. Okay? Nothing to do with the porcine, and this guidance applies on both sides.

It has a big advantage to be homogeneous because there are certain heterogeneity between these two, this one being the most severe.

Okay. Next.

Now, for preventing the background in Europe, assuming you source your bones in Europe, but for sourcing locally and for importation, the same concerns apply. And here I have listed without making the reference because that would be an end of this, there is a total feed ban, and according to the countries, well, Britain started in '88, Switzerland, France, and Netherlands, I believe, in '90, and so on

and so on.

Meat and bone meal then now complete for all animals, contrary to what the States have, by calcium phosphate, selective ban of fat, et cetera, et cetera.

There is a testing program going on now in the various countries for all animals at risk like foal and stock and things like that, and also for isle (phonetic) animals more than 30 months. This is going to be brought down to 24 months. Destruction of the affected animals to herds and so on, removal of specified risk manure materials.

Now, also once going further, ruminant byproducts no longer allowed as fertilizer, meat and bone meal, and still in certain places one can use dicalcium phosphate as fertilizer, but not everywhere, and anyway, commercially the people don't want it anymore.

There is this important classification according to the BSE risk of the various countries which should be documented, and that's available. The full document is available on the Internet.

There are trade restrictions, and that's specifically for gelatin. Only porcine gelatin is still allowed in animal feed for vitamin concentrates.

All the rest, gelatin is forbidden also for animals just not because it has been shown that it could be dangerous to avoid any cross-contamination with other proteins, et cetera, and to make sure.

Thank you.

This is the rule for the food gelatin -- I don't know. I still have a few minutes -- for the food gelatin in Europe. So it's eight parts in this rule, and it's dealing with the old description of the establishment, the raw materials, the transportation of these raw materials, how you manufacture the various process, bacteriology, residue of final product, packaging, storage, importation of third country requirement, and there is a lady there who has been suffering on this when it was going about gelatin from the United States, and commercial documentation that has to follow with the goods every time.

For BSE, there are two chapters concerned: source of raw materials and process to be used, saying roughly that these are the existing four categories of countries, BSE free, provisionally BSE free, low BSE risk and high risk.

High risk is forbidden anyway, and that's typically a U.K. particle. Low BSE risk number three is the only one which requires in this chapter that

you use only an alkaline process based on earlier results showing that alkaline process has a higher deactivating potential vis-a-vis TSE.

And of course, raw material, the source is also influenced. So you cannot take from U.K. You preferable take from Category II countries, I or II.

Next.

That was for the food. Now, very important is the issue of the pharmaceutical gelatin. So the EMEA note for guidance, first issued in '92 and revised every so often till 2000, says several things, and its rules was a lot of common sense, practical common sense.

When possible, first -- it is a summary, of course -- avoid ruminant material. Okay, but is good to say. The risk can be greatly reduced by controlling three things, and that is where they insist very much that you cannot just insure safety on the grounds of either the raw material or the tissue that you use or the process that you use. You have to look at the three different things before you can say we're feeling safe and comfortable with the story.

So the country of origin and they issued this before these categories were brought in. So that's why it doesn't take the four categories here,

but, say, no BSE plus a series of conditions. Then it's okay, most satisfactory. You can use also from low BSE case country like you have in European continent, providing another series of conditions, or from high incidence, provided closed herds and things like that.

So that's, again, the same as for the food, but expressed in a different way and slightly tighter.

Nature of tissue, prefer Category IV. You have in the World Health Organization publication a summary of the infectivity of the various tissues where high infectivity all the way down to never infectivity being identified. Of course, that is the one which is preferred. That's the one where in Category IV you find the actual bone tissue. I'm not talking about marrow, and the skin tissue.

And of course, avoid cross-contamination. That's especially that.

Production process, they say you should carry out validation studies on your process to see. They have -- this is the general thing. They also give for a series of products special rules, and there is a little chapter about the gelatin, and they take all of these details, again, but giving skull, spinal

cords, spines depending on the geographical risk. So not always, but they also ask for some practice. Should be ISO 9030 certified for quality; should be HACCP applied for the BSE and cross-contamination risk, and so on.

Traceability, audit of supplies, all the system. Okay.

For bovine hide, there is less concern. They just say avoid cross-contamination, but because of the slaughtering practice, that after the head is cut off of the animal, the skin is the first thing taken away before any other carving. There is very little risk there, and the skins are very much washed and treated with lime and salt, et cetera, before they can go further. So there is quite less concern on that.

An important thing with these little stars here is that this rule says that the manufacture of the product, in this case the gelatin manufacturer, should present a risk assessment, that is, how much infectivity might you have in your product and how often would it occur, say, in a year's time that you have infected material getting in your system and getting out.

That's what you all have to present and

make nice, fat dossier in order to be examined by the European Pharmacopeia, allowing you to say this is certificate of suitability. We can use this.

Nearly all, yeah, ruminant gelatins manufactured in Europe have been through this exercise which is lasting now for a few years. There are also non-European manufacturers who have been through this exercise, especially Japanese and Indians are trying, but with less success, and so on.

The older products and the companies having a certificate of suitability, according to this procedure, are also available on the Net, on the site of the European Pharmacopeia.

Thank you.

Well, just to conclude the brief summary of the action and DME believes that they have been proactive taking measures, as you can see, starting in 1990 we already start talking about the scientific bioassay to check whether there is any infectivity or whether it would be reduced to the process.

We discussed in '91 with the members, with experts, and the European Commission about a study design, what is available. Here this say the animals for bioassay susceptible to this or this type of transmissible spongiform encephalopathy were not

available like today ten years ago.

We make a presentation and discussion after big BSE convention in Heidelberg on the same subject. The start of the first was done in Inveresk, Scotland in '93 just with the chemical treatment. In '94, GME committed themselves for standard conditions both on the requirement of the German government and also vis-a-vis the FDA, and Dr. Chiu spoke about the '84 meetings here.

In '95 there was a study carried out full scale with noninfectivity, but it's an important one. On the degreasing of the bones, the fresh bones crushed, washed, et cetera, or finally dried. This degreasing operation removed potential nervous tissue. How much? Nobody knew really because there is a little fat left, of course, and it appeared that it removed close to 99 percent of nervous tissue that could be there as measured by some specific trace of proteins. So it's an important thing.

Yes, thank you.

'96, and that was '96. March '96 was the panic with the human cases in Britain. We start a repeat study in Inveresk, and it was second and third. The second was just a repeat. The third was adding two operations to see whether not only mathematically,

but also whether physically and chemically the two operations' efficiency to remove infectivity would add up, and apparently they do at the accuracy of the measurements.

In '97, before specified risk material was compulsory removed from all of the ruminant products, GME managed within their 11 members to agree to remove no use of any skulls anymore. Then they did similar things with the spinal cord and so on every time before the authority imposed it.

There was a decision to exclude spinal cord in '98, and in '98 we got the results of this study, received two years necessary for the animals,and in '99 we start a comprehensive study.

Dr. Chiu said that that one has to look into how the study was designed. The protocol of the projects have been submitted to a series of experts, and we have altered -- there have been several issues, and so on. The latest one is dated November '99. It involves, amongst other, the basic principle that we should look also to physical operations within the process, and that we should run all from a fresh bone, well, with whatever's left on it, including the marrow, with the highest possible infectivity brought in; goes through the whole process all the way down to

the gelatin and see whether there is anything left, provided you put to start with a very high infectivity level.

This infectivity level that was put systematically in it was about ten to the fifth power of the infectivity that would represent the worst case, that is, that you use only spines with the spinal cord and only from infected animals. So the infectivity we put in there was about ten to the fifth.

And now I think Dr. Rohwer, who has everything in his hands, will give the more scientific part of it, and I'm certainly looking for it.

Thank you.

CHAIRMAN BOLTON: Thank you, Dr. Schoentjes.

Are there any questions before we move on to Dr. Rohwer? Yes.

DR. CRAWFORD: Yes, my question is twofold. One is are there non-members of GME, and if so, what percentage do they export to the U.S.?

DR. SCHOENTJES: There is one company making similar to gelatin product, but it's more like hydroysates (phonetic), and I don't know that they export anything to the U.S., and certainly not for the

capsule industry. Otherwise all of the European produce for our members there.

DR. CRAWFORD: The second thing is are these regulations that the U.S. promulgated rigidly enforced. Are there inspectors in the plants or are these just guidance to the industry?

DR. SCHOENTJES: Oh, no. Most of them are now rigidly implemented. One thing one should see, these European regulations, they are so-called decisions. That means that they have to be translated in national law in between the member states are allowed not to apply it from strictly legal point of view.

In practice, because of the open markets, they are actually applied by the companies or the citizens, say, because otherwise they cannot do their within Europe business. And I give, for instance, the example of importation of goods. There is no border, say, between France and Germany anymore, which is good news, and that means that if the regulations are different, there is no control there. There are no customs officers and veterinarian checking.

But if you go in Hamburg or in Marseilles and you import from third countries, they will not apply only the national rule. They will apply the

European rule because the man in Hamburg is responsible of what's being imported in France and vice versa.

So in practice, these European rules are being applied very quickly.

DR. CRAWFORD: So how many countries have adopted the rule?

DR. SCHOENTJES: Well, most of this rule are adopted within the year that they're published.

DR. CRAWFORD: Then of the countries have or 15 or how many?

DR. SCHOENTJES: Oh, yeah.

DR. CRAWFORD: At the national level.

DR. SCHOENTJES: Out of the 15, we can give a figure. Reiner (phonetic), help.

PARTICIPANT: Fourteen.

DR. SCHOENTJES: Fourteen, yeah.

CHAIRMAN BOLTON: Stan.

DR. PRUSINER: Thank you for a very interesting presentation. I was a little misunderstood yesterday, and I was glad that Steve DeArmond corrected that in terms of what I really care about. I really care about all people. I care about individual European people and their health every bit as much as I care about American people and their

health. The issues of business are slightly different when I hear what I heard yesterday.

I'm just curious, and in a perfect world, and let me just throw this out, and I'm very interested in your reaction, I mean, I see that the vast bulk of gelatin ends up in film, not for photographic uses. Now, that's a huge sink. In a perfect world, wouldn't it be that you would take European gelatin and use it for photographic film, and you would take another country where there is no record of BSE or an area where there is no record of BSE, and you would use that for all the capsules whether it's Europe or the United States or wherever it is?

And I'm just curious whether your association has ever sat down and really thought about this in global terms like that or whether this is just something that is beyond anything that you guys think is practical.

DR. SCHOENTJES: We certainly think about it globally. That's certain. Now, the gelatin industry is really also a global business worldwide. That's for sure. But looking at the size of the business, it's, in fact, fairly small in terms of, you know, cash, and the way of photographic industry as

compared to gelatin industry. So much larger; the pharmaceutical industry is so much larger.

The gelatin industry hasn't much of a say in this area, and that's why we cannot so much influence when we would say we'd like to put to the photographic industry these bones which are less safe, et cetera. They would say, "No. We paid for it. So we need it."

And they can make the decision. Moreover, they are integrated. They have their own gelatin certainly in the States. They have their own gelatin manufacturing, huge plants, and they have a pressure, say, that the gelatin manufacturers don't have the same way.

The second thing is that in our plants, in a plant where we manufacture this type of gelatin, one manufactures both for photography and for pharmaceutical, slight process difference with a chemical somewhere else. So nothing else.

We don't want to have this second class raw material getting in the same place. So we want to have everything suitable for pharmaceuticals, and photographic gelatin is not safe, suitable for food or for pharmaceutical, but in practice, look at the specifications. It's okay.

And not here in the States, but in Europe, we also have questions from Occupational Health and Safety. They say we are making photographic film. We are handling bags of gelatin. Show that it's safe, that we don't get any BSE because we're handling the gelatin.

So we don't have, say, a nice and a dirty line. No, we want to have everything spic and span. That's the attitude we have.

DR. PRUSINER: If only practice and attitude were totally the same.

Thank you.

DR. EWENSTEIN: Yeah, it was maybe sort of a technical question, and I'm sorry if it's naive, but not all gelatin goes through an alkaline process or is that incorrect? In the manufacturing, there's an acid. There's an acidification process and an alkali process, but is that universal or are there certain gelatins made without the alkali process?

DR. SCHOENTJES: Oh, no. Nothing is universal. All the company manufacturing bovine bone, all use at least the alkaline process. Some of the companies manufacture according to the alkaline and according to the acid process, usually in dedicated specific lines, but, yeah, that's the straight answer.

Both processes give different TSE reductions in the factor, and the choice of the one or the other depends on the downstream use of the gelatin because chemically they're not the same, and physically they're not the same either.

CHAIRMAN BOLTON: Dr. Belay.

DR. BELAY: Yes. I'm trying to understand the current practice better. For the bones that you're sourcing from within Europe, I think I heard you say you exclude the skull bones from the bones that are currently collected from the European countries. So you exclude the skull bones, right?

DR. SCHOENTJES: Yeah.

DR. BELAY: And do you also exclude the spines or the vertebrae?

DR. SCHOENTJES: Now we have to do it, yes, right.

DR. BELAY: Okay. Now --

DR. SCHOENTJES: Certain do; certain don't, but I think it's difficult to say because that depends on the country and on the member companies. European regulation says you have to. It has not been translated in old domestic, but certainly the gelatin manufacturers, when they use European bones and they intend to use it for food or pharmaceutical, they make

sure there is no vertebrae in there.

DR. BELAY: Now, practically, how feasible is it to sort out the spines in this card? Now, I can picture a pile of bones coming out of the slaughter house and how practical and how feasible is it to sort out the spines and the skull from this huge pile?

DR. SCHOENTJES: Okay. To sort out, the skills is very easy because, as I said, that's the first thing that is done after killing the animal, is to take the head off. It's immediately separated, and the whole head now is considered specified risk material, so including the eyes and everything. So that's all disqualified and finally incinerated.

For the spines, it's a quite different issue, and that's why it has been taking such a long time to actually be able to remove them or to enforce them. When the animals are taking head off, the skin is taken off. Then the belly is opened, emptied, and then they split the carcass in two, and they take the spinal cord out and take the fat, clean it, and so on.

The carcasses for being distributed around the place, all the way down to small butcher shops are for the sake of health reasons -- they are hung by the back foot up, and they're transported hung. So this half carcass is transport hanging, not on any floor or

surface.

If you take the spinal column out of it before you transport it all around, all of the meat will stretch out, get on the floor, and you cannot even sell it, at least for people are eating the meat in another way than ground meat, and ground meat is a typical American specialty.

Well, okay. It's a dentist issue probably.

(Laughter.)

DR. SCHOENTJES: So it is not possible doing that way. So in the text saying that now you have to take out the vertebrae as specified risk material, it clearly says the head is the first thing at the slaughter house. The spines or the vertebrae have to be taken out wherever it has been distributed, but it's very tough because then the rule also says that one that's separated has to be denatured, say, by staining, has been collected -- has to be collected in special containers, transported in special transport. It's not the same truck that's carrying the meat for food that can carry the specified risk material, and so on. So all of the logistics have to be put in place.

So that's really for, say, the government,

what they have to put in place to implement that. Now, as long as this is not fully implemented, what happens? In the bone degreasing operation, the renderers, they have the selected collections. They have these bones. These bones are going through a process where the first operation is to be washed and ground for washing, and that allows also to allow for the bone marrow to be taken out.

But prior to entering that, these bones are dumped on a big conveying belt, and there on the conveying belt, you have or you can have people sorting out the spines.

Actually that's fairly easy to be done because this sorting out is minor if you're not talking about the spines, but there is always at last one or two persons survey this conveying belt for any foreign material that may come with the bone.

Typically when you collect bones like that, you have stainless steel hooks from the butcher which come with bones. If that gets into the system, the grinder is dead.

You have, well, a piece of rope sometimes, a piece of plastic that can come with it, and so on and so on.

So there are people surveying before any

operation on this conveyor belt, and on several places that's where they take the spines out as well.

In the United States, it's easier when you have these big meat packers where all the meat is cut on the same location that the animal is slaughtered. The cow goes in and nicely packed meat is getting out of this other place. That is the most developed part of it.

In Europe it's not developed to that extent, and still here we have questioned the meat packers, all of us, to take the vertebrae out because today for food purpose at least, it's not allowed to use American bones any longer because the spine -- so we've been putting pressure on the meat packers, but they're not ready to do it because it costs money, of course.

CHAIRMAN BOLTON: Dr. Bailey.

DR. BAILEY: Yes. John Bailey, FDA.

Most of your discussion has addressed the issue of capsule gelatin. Could you comment a little bit on food gelatin, the production and export of food grade gelatin for food use from the EU into the U.S.?

DR. SCHOENTJES: Well, to the best of my knowledge, Europe is not exporting food grade gelatin to the States or it's really very minor. The United

States are quite self-sufficient.

Well, the United States plus what's imported from Mexico and from Latin America in general, from Latin America, well, from Mexico it's pig skin, and then if you go further south, it's mainly bovine hide gelatin.

CHAIRMAN BOLTON: Dr. Lurie.

DR. LURIE: A follow-up on Stan's question about the fate of American bones, I suppose, something of concern to all of us. I guess in looking at the data that you provide it seems quite clear to me that the number or the metric tons of American bones used is more than enough to satisfy the requirement for capsules and pharmaceuticals in this country, and that if you chose to, you could satisfy all of the American capsule and pharmaceutical needs strictly through American bones. Is that not right?

DR. SCHOENTJES: No, no, because a good deal of these American bones, they're produced -- they're less than a handful of bone produced in America, and everybody is competing on it, including the photographic industry worldwide and the gelatin industry worldwide.

Japanese buy American bones for making their pharmaceutical products in Japan for the

Japanese market, and everybody is competing for this.

DR. LURIE: Right. So if somebody is willing to pay more for an American bone, in other words --

DR. SCHOENTJES: Sorry. I didn't get that.

DR. LURIE: If somebody is willing to pay more for American bone, it will wind up, say, in a photographic plate, whereas in the alternative it might wind up producing a safer pharmaceutical for an American; is that right?

DR. SCHOENTJES: It might, yes, but there is no specific reason for that because, in fact, American bone is the large, recognized, safe bone today, but if you look -- well, our reference, of course, is European Commission, the Scientific Steering Committee, and when you look to the classification of the various countries that we have, that's for animal health, of course. We see that except for all the countries with quite a number of case on the continent, America or Sweden or Austria assume the same risk for BSE in the cattle, and hence, in the cattle bones, and the same for India or Pakistan.

So we feel there is no more harm, more

considering the process also which will reduce possible infectivity and the removal also of spines. If you're sure that you have no cross-contamination with nervous tissue or the tissue carrying infectivity, American cattle bones are not more attractive than others.

It happens that the pharmaceutical industry, the capsule manufacturers, are controlled by the pharmaceutical industry, and these are major American companies, and that's why they are domestic American bone.

CHAIRMAN BOLTON: Peter, I think it's a combination of existing contractual arrangements and economic and business forces that are already in play.

DR. SCHOENTJES: Yeah, yeah, yeah.

CHAIRMAN BOLTON: It's not necessarily a health and safety issue as much as it is an economic and business.

DR. LURIE: That's my point.

DR. SCHOENTJES: May I make a comment? Yes, there is a big economic issue, and we as manufacturers individually, and as a member of GME, we try and take all necessary measures to make sure that under this economical pressure, we make every product safe.

And as you've seen from the historical recap there, we've been looking into this process efficiency, especially because we are not mastering 100 percent the raw material source. We cannot say we just make safe things, and then we can do whatever we want in our plant.

No, we want to be our plant -- possible additional warranty if we cannot control all of the raw materials.

CHAIRMAN BOLTON: Any other questions? Oh, Dr. Ewenstein.

DR. EWENSTEIN: So I just want to make sure I understand this idea of food grade gelatin versus pharmaceutical grade. Obviously they're both for human consumption.

I know in this country we have this funny distinction, you know, that there are certain things that can't be regulated. Maybe they should be, but they're not while other products are.

But from what I think I'm hearing from you is that from your point of view you manufacture them all to a certain standard even though the regulations would be different in this country, or do you have different levels of certification for yourself for products that are going to wind up being food versus

pharmaceuticals?

DR. SCHOENTJES: No. In most plants of my company, and I guess from the other members, we manufacture on the same plants food and pharmaceutical grades gelatin. That means that the plant and operation and raw material should comply, in fact, with both, whatever is the most demanding. That is the general trend anyway.

How should I say? Even for the graphic gelatin, you can put it in confectionery with no problem.

CHAIRMAN BOLTON: Any other questions? From the floor.

MR. TURNER: I'd like to give some extra information because I might have the feeling that you might understand some issues not quite correct, and that is --

CHAIRMAN BOLTON: Would you introduce yourself?

MR. TURNER: Yes. My name is Dick Turner from Holland, and I'm a member of the GME.

But especially the case of the removal of the vertebrae is in some countries absolutely the case. We don't get any removal vertebrae in our facilities. There are only a few countries who are

not applied the European regulation, who might have difficulty with that, and they have to do with other plants.

There are certainly a lot of countries who have implied the removal of the vertebrae and there is absolutely now you can expect no vertebrae coming into our facilities.

Thank you.

CHAIRMAN BOLTON: Thank you.

Another comment from the floor?

MR. SCHRIEBER: Yes, I'm Reinhard Schrieber, from GME just to clarify two further things.

The question came along with regard to acid bone gelatin. So the total quantity of acid bone gelatin manufactured for pharmaceutical applications is about between two and three percent of the total gelatin manufacture, bone gelatin manufacture for these applications.

This has a few special applications for special types of capsules. So it is reduced to the minimum necessary because we are very keen, of course, to maximize the production of alkaline treated gelatin,b ut for special cases, there is still a need, and what we will hear later on, we have developed

already a new process to increase the safety of this type of product, as well.

Then I'd like to address another point with regard to the use of U.S. bones. First of all, about 50 percent of the total U.S. bones available are taken by Kodak here in this country. So they absorb this. That's number one.

Number two is that our industry, the gelatin industry, making food and pharmaceutical gelatin here and in Europe has increased the use of U.S. bones over the last five years by more than 50 percent.

So we have really pushed the meat packing industry in the United States to produce more and more bone chips for our industry because the demand was growing, and we are keen to get as much as possible, but what we have reached now basically I think is the maximum we can reach. So we have really pushed them ahead to manufacture more and more, but now we are up to the top level, though only beef consumption increase could help us to get more U.S. bones out of this market here.

(Laugher.)

MR. SCHRIEBER: Well, that's a fact.

Thank you.

CHAIRMAN BOLTON: Thank you, Reinhard.

MR. LURIE: That's a comment that comes from the Beef Council of the U.S.?

CHAIRMAN BOLTON: Are there any other questions?

Okay. Thank you, Dr. Schoentjes.

We'll move on to a presentation by Dr. Bob Rohwer, who will talk about the inactivation study and overview and results, and these are preliminary results, I think, at this time.

I guess another option would be to breed cattle with more bones and less meat.

DR. CLIVER: We're doing that in India and Pakistan already.

(Laughter.)

DR. ROHWER: Well, I'm back again. I'm not sure how late you all were here last night. I snuck out around seven. But I hope this doesn't turn into the same kind of thing today. I don't think it will.

I want to preface my remarks about this really very large study that GME put together by just stating again emphatically that this is work in progress. There have been no final reports issued for this study yet. Animals could still get sick in these

titrations that are ongoing. The numbers could change a little bit for the more advanced studies, and they could change quite a lot for the less advanced studies.

So we're not going to talk about the less advanced studies. I'm only going to show you the things that have developed to the level of a year or more of incubation where the changes should be minor between now and the conclusion of these studies.

If I could have the first slide, I thought in listening to Dr. Schoentjes that it might be useful, especially useful, to go over some of the gelatin manufacturing industry from my perspective. I'm not a gelatin expert, and I'm becoming more and more one as time goes on, but I also get confused about the really tremendous complexity of this industry, and so I'm just going to point out a few things which I think might be helpful to you and get us oriented before I start presenting this data.

One, gelatin is its collagen basically. It's a soluble, high molecular weight hydrolysis product of collagen, and we all know that collagen makes up skin. People don't think about it, but it's actually a major component of bone as well.

And so the source can be either bones or

hides, and as was mentioned earlier, either cattle or pigs. These are the animals that are usually used for production of gelatin, but it can actually be made from any kind of collagen, any collagen source.

And then you have these various processes which there's an acid process, an acid-alkali process, and these processes are pretty prototypical. I like to think of them kind of in the way that I think about the cone fractionation for plasma products. It's a fairly standard thing, but every producer has their own little nuances which they jealously guard with IP in the manufacture of plasma products, and that's also true in the gelatin industry as far as I can tell.

And so there are variations, and so some of the process parameters can vary a little bit, and in ways that are hard to appreciate as an outsider to the industry.

And then there are multiple, multiple uses for these materials: food, capsules, excipient stabilizers. Gelatin is used very pervasively in both our biological type products, but also industrially in these types of things.

Next.

And the GME we just heard represents a very large proportion of the world manufacturing

capability. Forty-five percent, I think, is the number I just saw in Dr. Schoentjes' slides, and as such, they were interested in looking at this question.

But in order to look at it in a representative way, they had to come up with a protocol that represented the entire spectrum of their industry as much as possible, and so what was developed was a generic protocol and with a number of different arms to it, trying to draw in as much of the spectrum of production as possible.

But it was mainly focused on bone gelatin, and so all of these experiments are based on the production of bone gelatin, not hide gelatin, and it was also focused on cattle derived gelatin for the obvious reason that that's where the perceived risk is.

Well, bone gelatin is used to produce high grade capsule gelatin. It's made from the collagen matrix of bone, which is called ossein, and I've made this analogy to the cone fractionation already.

Next.

So in developing the protocol, the various process parameters were selected by GME. They developed the actual process that was going to be

followed, and then once they had decided what they were going to do, the next big issue became one of scaling it down to a laboratory bench scale of experiment, and this was done in consultation with myself and David Taylor, though we were mainly sounding boards since we are not gelatin experts.

And I think it's important to note that this was a de novo process. There was no preexisting bench scale procedure. The gelatin industry has not been burdened with having to do virus validations and this type of thing that is required for registration of pharmaceutical products. They're not a pharmaceutical industry, and so this had to be developed de novo.

And the main requirement and the difficult aspect of this to overcome is that they had to start with bovine bone. This is because rodent bones are just too small to be realistic in a process like this. I imagine they would disappear in the first few steps.

And as a consequence, by starting with bovine bone in a realistic amount of bovine bone, which turned out to be about two kilograms, the volumes that were used in this experiment got quite large at times, and the manipulations got quite cumbersome on a laboratory scale.

And with the added requirement that we had to keep the biohazard issue under control, this became a fairly big task to develop this protocol. A lot of credit goes to Ed Grobben, who is sitting here in the audience, who spent, I believe, a good eight to 12 months, maybe more, working up the details of this protocol and adapting it to equipment that was scaled, finding the equipment and adapting the equipment to this protocol and doing it in a way that kept the biohazards under control.

We had to figure out how to do these things in benches in the laminar flow cabinet, how to support the -- another problem with doing a gelatin experiment is after a certain point, you have to keep everything at 60 degrees. Otherwise it solidifies, and so you're juggling this stuff which has to be kept warm and also in the cabinet at the same time.

We made a lot of use of tempering beakers and circulators and that type of thing to do this.

Next.

Logistically just doing the experiment was quite complex. Starting with bones, it takes over a month to complete a run to the final product because some of these incubation times, the acid incubation in the lining step are very lengthy. It's weeks.

And, again, you're starting with a large amount of bones, and then we had to address these issues. Containment. We also controlled cross-contamination, was also an issue for us, and that was managed by using all new, dedicated equipment for each line of the protocol, disposables wherever possible, and we did not reuse any equipment in this protocol that could not be sterilized by autoclaving in the presence of one normal sodium hydroxide.

We had some very nice stainless steel, German stainless steel for the filtration components of the experiment, for example.

Next.

There were two components to the experiment. One, the whole manufacturing process was monitored continuously from beginning to end; it was run continuously from beginning to end. It was spiked at the level of bone, carried all the way to gelatin, and this was done in Edinburgh under David Taylor's supervision at the Institute for Animal Health, Neuropathogenesis Unit.

And then at the end of the gelatin process, and I'll show you a diagram here in a minute so you can see how it's laid out, there are some purification steps which involve filtration, ion

exchange chromatography to remove impurities, and then finally a UHT sterilization step. UHT is the ultra high temperature form of pasteurization that's used, for example, to make the boxed milk that you can find on the grocery store shelf that doesn't have to be in the cooler. It sits there on the shelf. It's a very, very brief, seconds exposure to a relatively high temperature in a wet heat environment.

During the course of this study, it was decided to develop some experimental arms to look at some alternative processing methods which might produce higher levels of inactivation of the agent than the process itself.

One of these experiments was done by Bram Schroeder, under the supervision of Bram Schroeder in the Netherlands, and another one was done in Edinburgh, and I'll show you some data on those as well.

And finally, to maintain continuity through the entire experimental process, Mr. Grobben was present at all stages, first in Edinburgh, and then in Baltimore with us. He took copious notes and produced a lot of photodocumentation, which it was my plan to show you some pictures of this process, but the files were so large they were crashing my computer

last night, and I finally took them out. I was afraid we wouldn't get through the presentation.

So we're going to have to skip the pictures. So let's go on to a diagram.

Oh, relevance of this spike. I wanted to talk about that. One of the diciest issues that confronts the execution of a validation study with the TSE agents is that the only source of high infectious material is central nervous system material and, for example, it's very, very unclear whether brain homogenate is an appropriate and relevant material to look at in the context of a blood validation study, for example.

But in the case of this study, we had the great relief of being able to work with central nervous system tissue in a context where it was absolutely appropriate. It is most likely that the source of contamination of gelatin would come from central nervous system tissues, the spinal cord, the dorsal root ganglia surrounding the spinal cord, the skull, and cross-contamination at the time of slaughter with other bones from central nervous system sources.

So we could start with brain mass rates and homogenates completely guilt free in this

experiment.

Another issue is the strain of agent. Well, we planned to use the Hamster 263 strain, which is a scrapie strain of TSE, simply because it's very well characterized. It's convenient, and it's fast, and it develops very high titers. But its relevance to a BSE validation is really unknown.

On the other hand, I would like to point out now that we've been working with the mouse BSE strain that in some ways I think the hamster is more cow like in its presentation of disease than the mouse BSE strain that we're using, and that's mainly in its clinical presentation.

Mouse adapted BSE was also to be used. This is a strain that has only been around for a few years. It's relatively uncharacterized, and again, I always question the relative relevance of these two strains or the various strains. It's neither clinically or pathologically cow like in its presentation, but it was the BSE agent that was passed to this mouse.

I think the main point and the most important point to note here is that the experiments were done with two different strains, and that gives us the opportunity to look at points of convergence in

the strain data for verification that the clearance that we're seeing is actually reproducible and quite possibly extrapolatable to bovines.

Next.

Well, this is the process crammed onto a slide here, and we're going to look at a bunch of these figures over the next few minutes to see how the experiment was actually done, but let's go over this first just so you'll get an idea of what we did.

The main line right here is a representation of the alkaline process for making gelatin, and these excursions on the left here are variants of it that were also investigated.

So you start with bones which are crushed to about a couple centimeters in mean diameter, and they're taken through a degreasing step, which basically is to cook them in a soup and make a broth and skim the fat and remaining tissues off of the bones, and they're washed and rinsed very extensively at this stage and then dried in a hot air stream.

The bone chips themselves don't get particularly hot. They get up around 80 or 90 degrees, and that's monitored during this step, and then they're sieved and sorted to get rid of little, tiny fragments, and I'm not sure this was actually

done as part of this process. We can ask Mr. Grobben about that later if you want.

And then at that stage they are demineralized, and this is done with hydrochloric acid, and it's done in a batch process over several days' time where the most exhausted batch of hydrochloric acid from the previous batch that was run through the operation is used first to demineralize the bone, and then as it becomes exhausted, you ramp up the concentration of hydrochloric acid slowly until at the end you end up at about four percent hydrochloric acid, and it sits in that for at least two days or more.

And what this does is it dissolves the minerals out of the bone, and they go into the aqueous phase, and that aqueous phase is then processed to produce various phosphates or hydroxyapatite, or in the case of a plant I had the privilege of visiting, it's ashed and is used in making bone china in the Netherlands. This is the origin, I guess, of the "bone" in bone china.

At one point we will also look at this demineralized -- this demineralized product is also being looked at for residual infectivity.

Once the minerals are removed, you have

something that's called ossein, and this is a remarkable material for someone who's not familiar with it. It looks exactly like the bone, the original bone. The bone has not lost its shape at all, but it has the consistency of a rubber ball and is somewhat porous and quite elastic.

Going from the demineralized bone or the ossein, the ossein goes into a liming process, an alkali process. Now, this is traditionally done with calcium hydroxide or lime, a very cheap source of alkali in a saturated state. It's saturated, which means that as the lime is exhausted by the process, it's constantly renewing -- I mean, as the hydroxyl ions are exhausted by the process, it's constantly being renewed from the solid line that's in the bottom of the vat that's being mixed periodically with these vats of ossein.

And this is a process that goes on for weeks, three weeks, three weeks or more sitting in this lime process. Now, the problem with lime is that when this was first presented to the TSE community in the Heidelberg meeting in 1992, it seemed like, wow, how can anything survive that? You know, two weeks in an environment like that.

But if you'll remember the slide I showed

you yesterday looking at the efficacy of sodium hydroxide at various concentrations, there was a big drop in efficacy between tenth normal and hundredth normal sodium hydroxide.

Well, unfortunately lime is producing a pH just a little bit above a hundredth normal in concentration. It's borderline. It's in that gray zone, and so it wasn't clear, and it turns out from preliminary experiments that were done at Inveresk that this is not a highly inactivating procedure. It does get rid of a couple of -- a log or two of infectivity, but it's not what people had hoped for originally.

And the same can be said for the hydrochloric acid treatment, though I think we had perspective on that before that acid is not particularly destructive. Weak acid is not particularly destructive to these agents.

Once the liming is done, it's neutralized back to a pH five or so, and then it's rinsed exhaustively with water, and at that point it's pushed into the extraction process. It's been sufficiently hydrolyzed by this process, even though it still looks fairly intact, such that hot water can begin to extract the gelatin. The gelatin is soluble in hot

water.

And different grades of gelatin are defined by the temperatures at which they're extracted, and so the extract, you first get all of the gelatin you can get at 60 degrees and then you move to 70 degrees and then you move to 80 degrees, and as I recall, the quality of the gelatin goes up the warmer the water required to extract it, though ask the experts if you want to know more about that.

So between here and here, this was one arm of the experiment, was to spike at this level, at the level of bone, at the level of bone, and then carry this all the way through this process to the extraction step, and then measure the final product, the pooled final product from this extraction step for residual infectivity.

Now, once you have the soluble gelatin, it is then taken through a series of purification steps, which begins with a filtration, and this is a filter aid type of filtration. It's taken through a mixture of diatamaceous earth, cellulosis, and those kinds of depth matrices to remove particles and other impurities from the gelatin, and the product of the filtration is then taken through ion exchange columns, a cation column and an anion column, and these are

flow-through columns. It's not an absorb and a dilute type of ion exchange. It's an ion exchange used to absorb impurities out of the gelatin itself. The gelatin flows through the columns.

And then finally, the product is UHT sterilized. The UHT sterilization consists of sending it through a device in a closed loop of pipe which injects live steam into the gelatin as it's flowing through the pipe, and the rate of flow and the constrictions in the pipe develop the pressures needed to maintain the temperatures at 138 to 140 degrees Centigrade for a very short period of time, four seconds.

It comes out of that pipe into an evaporator. From the evaporator the solids are extruded in to a noodle type material. It's dries and milled, and that becomes the final product.

The steps that we investigated in our laboratory are right here, these purification steps. The production steps, the main production steps were investigated in the Edinburgh laboratory.

Let's go on to the next slide.

So there were several experiments that were done, eight in all, and I'm going to show you where each of these experiments are, and I'm going to

show you what the diagrammatic representation of each of them are so that you know what's in process.

Experiment one was a -- now I forgot to gray this out -- was an Edinburgh experiment where the bone was spiked with mouse brain macerate, and this was done by taking bone chips and 20 grams of mouse brain and essentially smearing them, smearing it all over the bones, and then taking a portion of that macerate and actually injecting it into a piece of spinal column from a calf, and then tediously and laboriously sawing that spinal column into pieces the size of bone chips.

This was our attempt to make it as realistic as possible in terms of what might have come into a process in the way of a contaminate.

The titer, the total titer of this preparation is about ten to the ninth, starting titer for the entire batch. It's then carried through this process. The demineralized bone , the acid from the demineralization step was carried through to hydroxyapatite, and that is being titered. It's underway. It won't be complete until next year some time.

The extraction process is well over a year into its titration, and the log reduction seen to date

has been about four logs over this entire process.

And the process was carried at Edinburgh -- oh, that's why. That's why. This process at Edinburgh was carried all the way through the purification steps as well. At this stage of the process, they've got 4.2 logs removed. This material, this same material -- this was not respiked -- was carried through the purification steps and this has also been inoculated and we'll be ready to talk about that some time in the autumn.

Next.

This was an experiment using the hamster scrapie strain instead of the mouse BSE strain, and hamster scrapie was used to spike, but essentially it's the same process, and this one is not as far along in Edinburgh, and so you can see the dates at which we expect to see results over here on the left.

This arm was not carried through to the end, and so we will only get this first leg through extractable gelatin out of this experiment.

Next.

And this experiment number three was performed to investigate the acid process. Again, mouse BSE was used, and this time it was carried through to the ossein stage, but the alkaline liming

stage was skipped, and we went directly from ossein to the extraction stage, and the results of that are about 3.7 logs reduction.

This is probably within experimental error of what was obtained for the alkaline extraction, which is a little surprising to me.

Now, I have a question which perhaps the GME folks can clarify at the end of this. I thought I heard Dr. Schoentjes say that the acid process is not used to produce food or medicinal gelatin, but I was under the impression that all of the experiments that we were doing here were to test the risks for food and medicinal products. So I guess I myself would like some clarification on that when we're finished here.

Nevertheless, the acid process was tested, and this is the result to date. This was also carried through the final purification, and that's a little bit farther behind this experiment, and so we'll be ready to talk about that in August or September.

Next.

Now, there were a couple of experimental processes were also tested. This was the same experiment that I just showed you, the acid process, except that once the ossein had been formed, instead

of carrying it through the liming process, which takes weeks, the ossein was exposed to .3 normal sodium hydroxide for two hours. Then it was carried through the hot water extraction process.

As you can see, this gave a much higher log reduction, which is somewhere around five to six logs, and indicating, as you might expect, that by simply pushing the alkaline concentration into the realm of known efficacy, you get a lot higher removal or inactivation.

Next.

Now we're going to switch to the Baltimore laboratory and the experiments that we did here in Baltimore. This probably makes sense to go to the next one first and then come back to this. I got these in the wrong order.

The experiment we did first was with hamster scrapie spike, and in this case we're only looking at the purification steps. So we're not looking at bone. This is a downstream spike.

What we're using here is crude gelatin obtained from production. So we're taking the gelatin at the same stage it would be at in the production process, but we are now adding hamster brain homogenate to the level of .1 percent to this crude

gelatin and then carrying it through the filtration step, the ion exchange steps, and the UHT sterilization -- well, and the ion exchange steps. This is done separately.

So in the case of these first two steps, it was carried through to the level of filtration and titered, and this should be a log ten removal actually. I got carried away there, and we removed about 1.6 logs of infectivity by the filtration step.

We then took this filtrate and passed it through the ion exchange column and looked at the total removal of the two steps together, and we got only an additional .2 logs of removal by doing that. Clearly, once you've removed whatever you're going to remove by filtration, the ion exchange step is not removing any additional infectivity.

This is borne out when we then took the filtrate and we spiked it with hamster scrapie. We again saw a minimal removal by the ion exchange step.

Next. Let's go back. Can I go back to -- yeah.

Now, we've done the same experiment using the mouse BSE spike, but this is not far enough along to report yet, but we are getting things that look vaguely similar.

Next.

To the best we can tell with the data we have to date.

The purification step -- the next thing we looked at was the UHT sterilization step. In this case we again had to start with freshly spiked material. In this case we used gelatin from production again, spiked it, and then carried it through the UHT step itself.

Now, this had to be done in a much more elaborate way than the previous two experiments. To make this work, we had to devise a means by which we could scale down this process in the laboratory so that we would get a four second exposure to 140 degrees Centigrade.

Now, I had done something like that when I did the experiments I showed you yesterday that were conducted in the '80s, and I knew from those experiments or expected from those experiments that this might give us significant levels of removal.

The reason I knew that is I had also looked at an 80 degrees Centigrade inactivation which had really inactivated very little of the infectivity even after an hour; a 100 degree inactivation, which did inactivate a couple of logs; and a 121 degree

inactivation.

I knew that in that experiment when I ramped up the temperature in my oil baths, it took me about 12 seconds to get from 80 degrees to 121 degrees, and by the time I had gotten to 121 degrees, I had killed virtually everything in those 12 seconds.

Thus, I expected that by taking this stuff to 140 degrees for four seconds, we would be on the road to inactivation, and we might see a significant inactivation.

The way we did this was we devised a means of putting the gelatin in a stainless steel capillary like this, sealed a thermocouple -- forced a very fine thermocouple into the capillary itself with the gelatin. So we've got a lead coming out here which goes to a recording thermometer; put a pressure relief valve on this side, which allows the gelatin to expand without having to introduce any air into this tube.

If you take a tube like this, even a stainless steel tube like this and seal it at both ends full of gelatin and plunge it into a 140 degree bath, it will explode. We tried that.

(Laughter.)

DR. ROHWER: And it's sufficient.

But so what we did is we put a pressure

relief valve on this side, which maintains a back pressure of about 100 psi on this column, which you can take easily. This thing, this column is rated to something like 5,000 psi.

The reason that I wanted to do the experiment this way is because of these reservations that I talked about yesterday about drying on surfaces, and the way in which this UHT process is conducted in reality is the liquid stream is forced through this pipe by a pump. There is no air in that pipe. The only thing that's introduced is live steam, which is not air. That's water, and it seemed to me there would be very little opportunity for the material to dry and find herbage in that way against the inactivating properties of the steam.

We wanted to reproduce that in our capillary, and that's why we went to great pains to make sure that this thing was completely full of gelatin from one end to the other before we did the experiment.

And what we sampled from this capillary is we cut the ends off and forced the material back out of the capillary, and that's what we measured. So anything that was happening out here at these ends where we had to join it with the thermocouple or join

it with the back pressure valve was ignored. Okay? We're looking at the gelatin that was inside here.

Next.

And, in fact, we did get a very significant level of removal by this step, 4.2 logs of inactivation this time, not removal, not just clearance.

Next.

Finally, there was one additional experiment that was conducted using this protocol right here. Again, it was BSE spike. The process was carried only to the level of the sieve and sort, to the bone chip level, and the bone chips -- these were degreased bone ships. So there was removal here, but then the bone chips themselves were autoclaved briefly at 133 degrees Centigrade and then extracted with hot water right out of this small autoclave to five a product which was then assayed.

And no animals have yet gotten infected from this inoculum at 400 days post inoculation, and so the sensitivity of the assay is about six and a half logs, and provided no animals do get sick, this will have offered about a six and a half log removal itself.

This is not a process that's being used.